A 5-year-old boy is brought to the emergency department due to recurrent, generalized tonic-clonic seizures over the past 24 hours. The patient has been having high fever and flulike symptoms for the past 3 days. He has a past medical history of febrile seizures at age 6 months. He takes no medications and has no family history of epilepsy. The patient's temperature is 39.4 C (103 F), blood pressure is 110/70 mm Hg, pulse is 112/min, and respirations are 10/min. He appears lethargic and does not follow simple commands consistently. His neck is supple. During the examination, the patient suddenly develops sustained, generalized tonic-clonic convulsions without fully regaining consciousness between episodes. Which of the following describes the mechanism of action of the most appropriate initial therapy for his seizures?

A. Blockade of presynaptic voltage-gated calcium channels

B. Blockade of presynaptic voltage-gated sodium channels

C. Enhanced postsynaptic chloride influx

D. Inhibition of presynaptic neurotransmitter reuptake

E. Inhibition of vesicle fusion and neurotransmitter release

Submit

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- A. Blockade of presynaptic voltage-gated calcium channels (8%)
- B. Blockade of presynaptic voltage-gated sodium channels (38%)
- ✓ C. Enhanced postsynaptic chloride influx (48%)
- D. Inhibition of presynaptic neurotransmitter reuptake (2%)
- E. Inhibition of vesicle fusion and neurotransmitter release (2%)

Omitted
Correct answer
C

48%
Answered correctly

10 secs
Time Spent

03/15/2020
Last Updated

Explanation

This patient has **status epilepticus**, possibly due to complex febrile seizures or infectious meningitis/encephalitis. Regardless of etiology, the initial drug of choice for treating status epilepticus is an **intravenous benzodiazepine** (eg, lorazepam), due to its efficacy and rapid onset of action.

Benzodiazepines enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) at the **GABA-A receptor**, a ligand-gated

This patient has **status epilepticus**, possibly due to complex febrile seizures or infectious meningitis/encephalitis. Regardless of etiology, the initial drug of choice for treating status epilepticus is an **intravenous benzodiazepine** (eg, lorazepam), due to its efficacy and rapid onset of action.

Benzodiazepines enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) at the **GABA-A receptor**, a ligand-gated ion channel. Allosteric attachment of benzodiazepines to the GABA-A receptor causes increased **influx** of negatively charged **chloride ions** in response to GABA binding. This leads to hyperpolarization of the postsynaptic neuron and suppression of action potential firing (anticonvulsant effect).

(Choices A and E) Presynaptic voltage-gated calcium channels mediate the influx of calcium into the axon terminal, promoting vesicle fusion and neurotransmitter release into the synaptic cleft. Gabapentin is an anticonvulsant that works by blocking voltage-gated calcium channels, thereby attenuating excitatory neurotransmitter release.

(Choice B) Presynaptic voltage-gated sodium channels open when the cell becomes sufficiently depolarized, triggering an action potential that propagates down the axon. Phenytoin blocks presynaptic voltage-gated sodium channels and can be used to prevent recurrence of status epilepticus due to its long duration of action. However, it has a slow onset of action, and patients in status epilepticus should be given a rapid-acting benzodiazepine first.

(Choice D) Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are examples of medications that prevent presynaptic neurotransmitter reuptake. They are typically used to treat depression and anxiety disorders.

Educational objective:
Intravenous benzodiazepines (eg, lorazepam) are the initial drug of choice for status epilepticus. They work by enhancing the effect of gamma-aminobutyric acid (GABA) at the GABA-A receptor, leading to increased chloride influx and suppression of action potential firing.

References

- Benzodiazepine pharmacology and central nervous system-mediated effects.
- Pharmacotherapy for Status Epilepticus.

Pharmacology Nervous System Seizures

Benzodiazepines enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) at the **GABA-A receptor**, a ligand-gated ion channel. Allosteric attachment of benzodiazepines to the GABA-A receptor causes increased **influx** of negatively charged **chloride ions** in response to GABA binding. This leads to hyperpolarization of the postsynaptic neuron and suppression of action potential firing (anticonvulsant effect).

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References

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Pharmacology	Nervous System	Seizures
Subject	System	Topic

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A medical student is observing a pharmacology experiment where drug A is being intravenously administered to a pregnant dog. Some parameters that are being recorded during the experiment include heart rate, blood pressure, pupil size, and uterine contractions. The following diagrams illustrate the measured parameters and observed changes after infusing drug A.

Which of the following best characterizes drug A?

A. Beta-adrenergic agonist

B. Alpha and beta-adrenergic agonist

C. Alpha-adrenergic agonist

D. Beta-adrenergic antagonist

E. Alpha-adrenergic antagonist and beta-adrenergic agonist

Submit

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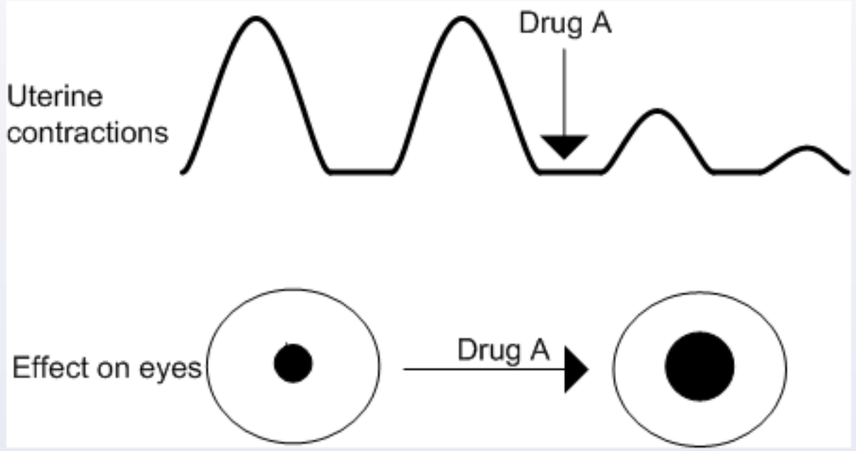

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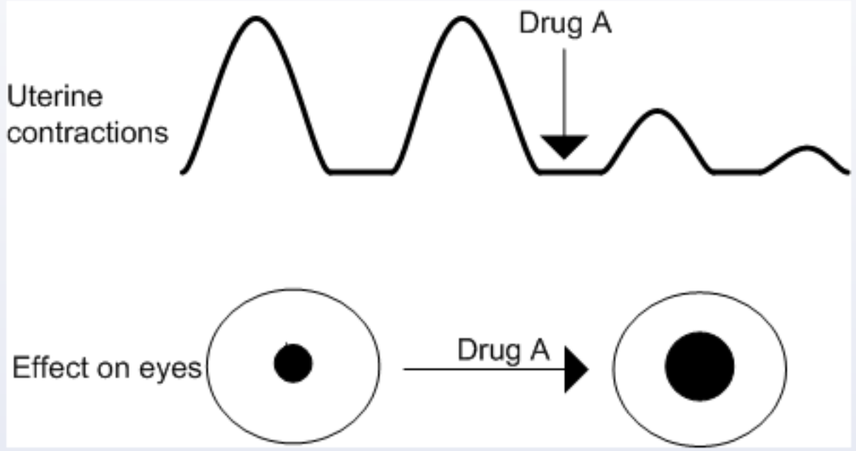

Which of the following best characterizes drug A?

A. Beta-adrenergic agonist (17%)
B. Alpha and beta-adrenergic agonist (43%)
C. Alpha-adrenergic agonist (15%)
D. Beta-adrenergic antagonist (7%)
E. Alpha-adrenergic antagonist and beta-adrenergic agonist (15%)

Omitted

Although the most pronounced effects of adrenergic agonists are those on the heart and vasculature, these drugs also affect many other organs. The graph above illustrates the effects of adrenergic stimulation on the eye and uterus. The pupillary dilator muscle of the eye possesses α1 receptors, and the stimulation of these α1 receptors results in contraction of the pupillary dilator muscle with subsequent dilation of the pupil (mydriasis). Ophthalmic preparation of phenylephrine (selective α-adrenergic agonist) is used to dilate the pupil before ophthalmoscopic examination.

Adrenergic receptors of the uterus belong to the β2 group whose stimulation leads to uterine relaxation (an effect called tocolysis) which is used in obstetrics to defer premature labor. Adrenergic β2 agonists such as ritodrine and terbutaline are used for this purpose. The drug in question, therefore, displays both α and β-adrenergic effects. See the table for the summary of end-organ effects of adrenergic agonists.

Receptor	Target organ	Effect of stimulation	Example
Alpha-1	Peripheral vasculature Bladder Eye	↑SBP Contraction of internal urethral sphincter Mydriasis (contraction of pupillary dilator muscle)	Epinephrine Norepinephrine Phenylephrine Methoxamine
Beta-1	Heart	↑HR, contractility and conductance	Epinephrine Dopamine Dobutamine Isoproterenol
Beta-2	Peripheral vasculature (skeletal muscle) Bronchi Uterus	Vasodilatation, ↓DBP Bronchodilatation Relaxation (tocolysis)	Isoproterenol Terbutaline Ritodrine

(Choice A) Beta-adrenergic agonists stimulate β2-adrenergic receptors of the uterus and diminish uterine contractions. They do not, however, affect α1-receptors of the eye and would not produce mydriasis.

(Choice C) Alpha-adrenergic agonists would produce mydriasis (α1 effect), but not uterine relaxation (β2 effect).

(Choice D) Beta-adrenergic antagonists block β2 receptors of the uterus and enhance uterine contraction. They do not affect α1-adrenoreceptors.

Alpha-1	Peripheral vasculature Bladder Eye	Contraction of internal urethral sphincter Mydriasis (contraction of pupillary dilator muscle)	Epinephrine Norepinephrine Phenylephrine Methoxamine
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(Choice D) Beta-adrenergic antagonists block β2 receptors of the uterus and enhance uterine contraction. They do not affect α1-adrenoreceptors of the pupillary dilator of the eye.

(Choice E) Alpha-adrenergic antagonist and beta-adrenergic agonist would cause miosis (pupillary constriction) and uterine relaxation.

Educational Objective:
Inhibition of uterine contractions (tocolysis) is a result of β2 adrenergic receptor stimulation. Alpha -1 receptor stimulation causes contraction of the ocular pupillary dilator muscle, resulting in mydriasis (pupillary dilation).

Pharmacology	Nervous System	Sympathomimetic agents
Subject	System	Topic

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Alpha-1	Peripheral vasculature Bladder Eye	↑DBP Contraction of internal urethral sphincter Mydriasis (contraction of pupillary dilator muscle)	Epinephrine Norepinephrine Phenylephrine Methoxamine
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Pharmacology	Nervous System	Sympathomimetic agents
Subject	System	Topic

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A newly developed inhaled anesthetic has an improved safety profile compared to traditional fluorinated anesthetics. Preliminary pharmacodynamic properties of the agent are determined through a series of experiments on human volunteers. The tests show that the agent demonstrates relatively high potency. Which of the following parameters best correlates with the potency of an inhaled anesthetic?

A. Arteriovenous concentration gradient

B. Blood/gas partition coefficient

C. Hepatic metabolism rate

D. Minimal alveolar concentration

E. Steepness of arterial tension curve

Submit

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- A. Arteriovenous concentration gradient (5%)
- B. Blood/gas partition coefficient (22%)
- C. Hepatic metabolism rate (1%)
- ✓ D. Minimal alveolar concentration (68%)
- E. Steepness of arterial tension curve (1%)

Omitted
Correct answer
D

68%
Answered correctly

01 sec
Time Spent

01/23/2020
Last Updated

Explanation

The potency of an inhaled anesthetic is determined by the minimum concentration in the brain necessary to achieve an adequate level of anesthesia. When an inhaled anesthetic is administered at a constant rate over a prolonged period of time, its partial pressure in the brain equals its partial pressure in the other compartments (inhaled air, lungs, and arterial blood). Since an anesthetic's concentration in the brain tissue is directly proportional to its partial pressure, it is possible to use the steady-state alveolar partial pressure of the inhaled agent as a measure of anesthetic potency.

The minimal alveolar concentration (MAC) refers to the percentage of anesthetic in the inspired gas mixture that renders 50% of patients unresponsive to painful stimuli. It corresponds to ED_{50} on the dose-effect curve. Potency is inversely proportional to the MAC: the lower the

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(Choice A) The arteriovenous concentration gradient is an indirect measurement of the solubility of the anesthetic in body tissues. A high arteriovenous concentration gradient means that more anesthetic is extracted from the blood by the body tissues, increasing the time it takes for the blood to become saturated and slowing the onset of action.

(Choice B) The blood/gas partition coefficient corresponds to the solubility of anesthetic in the blood. Anesthetics with a high blood/gas partition coefficient are absorbed to a greater extent by the blood and have a slower onset of action.

(Choice C) Clearance of inhaled anesthetics occurs mainly via exhalation from the lungs into the air; hepatic metabolism of most gas anesthetics is low. However, certain gas anesthetics, particularly halothane, are metabolized extensively by the liver, resulting in the production of reactive intermediates that cause hepatotoxicity.

(Choice E) The steepness of the arterial tension curve depends on the solubility of the anesthetic in the blood. Partial pressure in the blood rises more rapidly with less soluble anesthetics, producing a steeper curve.

Educational objective:
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Educational objective:
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Pharmacology	Nervous System	Efficacy and potency
Subject	System	Topic

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A 60-year-old farmer is brought to the emergency department due to acute-onset confusion, muscle weakness, and difficulty breathing. The patient has vomited twice and has had 3 loose bowel movements over the past 2 hours. His medical history is insignificant and he currently takes no medications. Blood pressure is 110/70 mm Hg, pulse is 58/min, and respirations are 26/min. His pupils are constricted, symmetric, and reactive to light. Examination reveals excessive sweating, lacrimation, and wheezing. He is incontinent of urine. Intravenous atropine is administered. Which of the following findings is most likely to persist in this patient without additional therapy?

A. Bradycardia
B. Bronchospasm
C. Diarrhea
D. Miosis
E. Muscle weakness
F. Urinary incontinence

Submit

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- A. Bradycardia (6%)
- B. Bronchospasm (11%)
- C. Diarrhea (4%)
- D. Miosis (11%)
- ✓ E. Muscle weakness (59%)
- F. Urinary incontinence (7%)

Omitted
Correct answer
E

59%
Answered correctly

01 sec
Time Spent

01/19/2020
Last Updated

Explanation

Cholinergic toxicity	
	• Diarrhea/diaphoresis • Urination

Cholinergic toxicity	
Muscarinic effects **(DUMBELS)**	• **D**iarrhea/diaphoresis • **U**rination • **M**iosis • **B**ronchospasm, bronchorrhea & bradycardia • **E**mesis • **L**acrimation • **S**alivation
Nicotinic effects	• Muscle weakness, paralysis & fasciculations

This farmer is exhibiting multiple signs of excessive cholinergic stimulation. He has likely been exposed to an **organophosphate**, a **cholinesterase inhibitor** that is commonly used in agricultural pesticides. Organophosphates inhibit cholinesterase in both muscarinic and nicotinic cholinergic synapses, leading to decreased acetylcholine degradation. Overabundance of acetylcholine within the synaptic cleft leads to overstimulation of the corresponding receptors.

This patient is currently experiencing the effects of widespread muscarinic activation, which increases visceral smooth muscle tone and glandular secretions throughout the body (**DUMBELS** mnemonic). Nicotinic activation leads to muscle fasciculations, weakness, and paralysis. Activation of both receptors in the central nervous system leads to seizures and coma. Atropine is a competitive inhibitor of acetylcholine at the muscarinic receptors, thereby reversing muscarinic symptoms of organophosphate poisoning. However, atropine has no effect on nicotinic receptors; patients are still at risk of **muscle paralysis**. **Pralidoxime** is a cholinesterase-reactivating agent that allows for degradation of excess acetylcholine and treats both the muscarinic and nicotinic effects of organophosphates.

(Choices A, B, C, D and F) Bradycardia, bronchospasm, diarrhea, miosis, and urinary incontinence are symptoms of excessive muscarinic activation, and are reversed with atropine.

Educational objective:
Organophosphates inhibit cholinesterase in both muscarinic and nicotinic cholinergic synapses, leading to decreased acetylcholine degradation

	• Lacrimation • Salivation
Nicotinic effects	• Muscle weakness, paralysis & fasciculations

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Educational objective:
Organophosphates inhibit cholinesterase in both muscarinic and nicotinic cholinergic synapses, leading to decreased acetylcholine degradation and overstimulation of the corresponding receptors. Atropine reverses muscarinic effects but does not prevent the development of nicotinic effects such as muscle paralysis. Pralidoxime is a cholinesterase-reactivating agent that allows for degradation of excess acetylcholine and treats both the muscarinic and nicotinic effects of organophosphates.

Pharmacology	Nervous System	Organophosphate poisoning
Subject	System	Topic

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A 25-year-old woman with newly diagnosed seizures comes to the emergency department with fever and skin rash. She had her first seizure 6 weeks ago, and an MRI of the brain revealed no structural lesions. She was started on phenytoin 4 weeks ago. Her temperature is 38.9 C (102 F). There is a diffuse confluent erythema involving 60% of the body, palpable generalized lymphadenopathy, and symmetrical facial swelling. Which of the following laboratory findings is most likely to be present in this patient?

A. Antineutrophil cytoplasmic antibodies

B. Blasts cell with Auer rods

C. Cryoglobulinemia

D. Eosinophilia

E. Microangiopathic hemolytic anemia

Submit

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A. Antineutrophil cytoplasmic antibodies (18%)

B. Blasts cell with Auer rods (4%)

C. Cryoglobulinemia (11%)

✓ D. Eosinophilia (47%)

E. Microangiopathic hemolytic anemia (17%)

Omitted
Correct answer
D

47%
Answered correctly

01 sec
Time Spent

07/04/2020
Last Updated

Explanation

This patient's cutaneous and systemic findings after recently starting a new medication suggest drug reaction with eosinophilia and systemic symptoms **(DRESS) syndrome**. DRESS is a rare and potentially life-threatening drug reaction typically occurring 2-8 weeks after drug exposure. Commonly associated drugs include **anticonvulsants** (eg, phenytoin, carbamazepine), **allopurinol**, sulfonamides (eg, sulfasalazine), and antibiotics (eg, minocycline, vancomycin). Although the exact mechanism is unknown, it likely involves drug-induced herpesvirus reactivation followed by clonal expansion of T cells that cross-react with the drug.

Patients typically develop **fever, generalized lymphadenopathy, facial edema**, and diffuse morbilliform skin rash that can progress to a confluent

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Patients typically develop **fever, generalized lymphadenopathy, facial edema**, and diffuse morbilliform skin rash that can progress to a confluent erythema with follicular accentuation. Other affected organs can include the liver (hepatomegaly, jaundice), kidney (acute interstitial nephritis), and lung (cough, dyspnea). Laboratory studies usually show **eosinophilia**, atypical lymphocytosis, and elevated serum alanine transaminase. Clinical findings improve over several weeks following withdrawal of the drug.

(Choice A) Drug-induced antineutrophil cytoplasmic antibodies-associated vasculitis is most commonly linked to medications for hyperthyroidism (eg, propylthiouracil, methimazole) and hydralazine. Patients can develop constitutional symptoms, arthralgias/arthritis, and cutaneous vasculitis.

(Choice B) Blast cells with Auer rods indicate acute myelogenous leukemia. Patients typically develop complications of pancytopenia, including fatigue (anemia), fever due to infection (neutropenia), and ecchymosis or epistaxis (thrombocytopenia).

(Choice C) Mixed cryoglobulinemia is a small- to medium-vessel vasculitis caused by circulating immunoglobulin-complement complexes that precipitate on refrigeration. It is typically associated with chronic inflammatory states (eg, systemic lupus erythematosus, hepatitis C) and can present with systemic findings (eg, fatigue, arthralgias, myalgias) and palpable purpura in the lower extremities due to cutaneous vasculitis.

(Choice E) Microangiopathic hemolytic anemia usually presents with anemia and fragmented red blood cells (schistocytes) on the peripheral smear. It has been associated with cancer chemotherapy drugs (eg, cisplatin, cyclophosphamide).

Educational objective:
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome typically occurs 2-8 weeks after exposure to high-risk drugs such as anticonvulsants (eg, phenytoin, carbamazepine), allopurinol, sulfonamides (eg, sulfasalazine), and antibiotics (eg, minocycline, vancomycin). Patients typically develop fever, generalized lymphadenopathy, facial edema, diffuse skin rash, eosinophilia, and internal organ dysfunction.

References

- Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the

lung (cough, dyspnea). Laboratory studies usually show **eosinophilia**, atypical lymphocytosis, and elevated serum alanine transaminase. Clinical findings improve over several weeks following withdrawal of the drug.

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(Choice E) Microangiopathic hemolytic anemia usually presents with anemia and fragmented red blood cells (schistocytes) on the peripheral smear. It has been associated with cancer chemotherapy drugs (eg, cisplatin, cyclophosphamide).

Educational objective:
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome typically occurs 2-8 weeks after exposure to high-risk drugs such as anticonvulsants (eg, phenytoin, carbamazepine), allopurinol, sulfonamides (eg, sulfasalazine), and antibiotics (eg, minocycline, vancomycin). Patients typically develop fever, generalized lymphadenopathy, facial edema, diffuse skin rash, eosinophilia, and internal organ dysfunction.

References

- Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study.
- The DRESS syndrome: a literature review.

Pharmacology	Nervous System	DRESS syndrome
Subject	System	Topic

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A 44-year-old woman with a history of breast cancer comes to the office due to persistent back pain. The patient was recently started on radiation treatment for several vertebral metastases. She has taken acetaminophen and nonsteroidal anti-inflammatory drugs but continues to have severe pain. On physical examination, she has tenderness over several lumbar vertebrae. Neurologic examination is unremarkable. The patient is started on oral morphine therapy. Which of the following is the most likely direct effect of this medication on the spinal cord neurons of this patient?

A. Activation of sodium-calcium exchange mechanisms

B. Blockade of voltage-dependent sodium influx

C. Increased calcium influx into the cells

D. Increased chloride influx into the cells

E. Increased potassium efflux out of the cells

Submit

A 44-year-old woman with a history of breast cancer comes to the office due to persistent back pain. The patient was recently started on radiation treatment for several vertebral metastases. She has taken acetaminophen and nonsteroidal anti-inflammatory drugs but continues to have severe pain. On physical examination, she has tenderness over several lumbar vertebrae. Neurologic examination is unremarkable. The patient is started on oral morphine therapy. Which of the following is the most likely direct effect of this medication on the spinal cord neurons of this patient?

- A. Activation of sodium-calcium exchange mechanisms (5%)
- B. Blockade of voltage-dependent sodium influx (35%)
- C. Increased calcium influx into the cells (5%)
- D. Increased chloride influx into the cells (17%)
- ✓ E. Increased potassium efflux out of the cells (36%)

Omitted
Correct answer
E

36%
Answered correctly

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01/10/2020
Last Updated

Explanation

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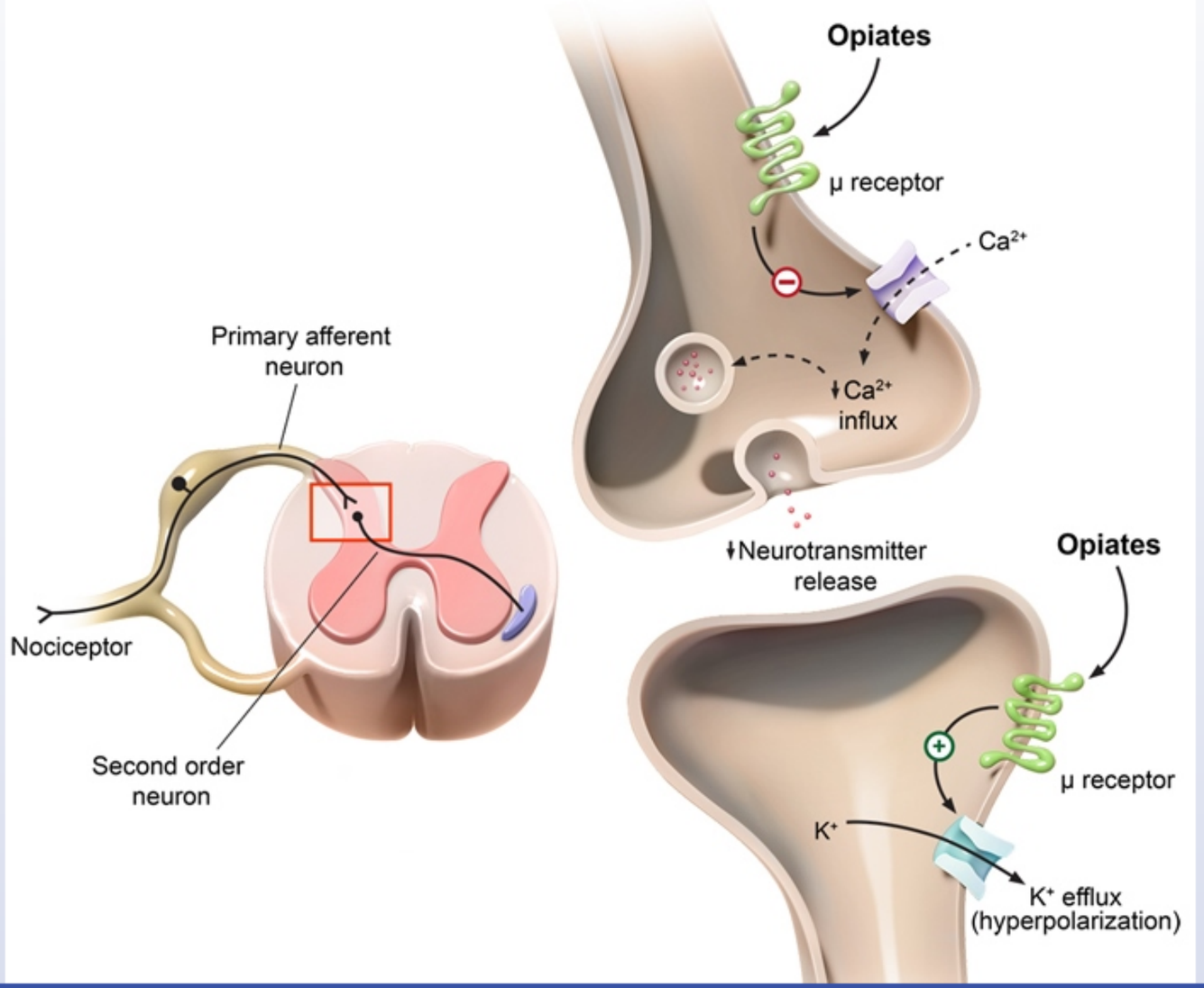
Opiate-induced analgesia



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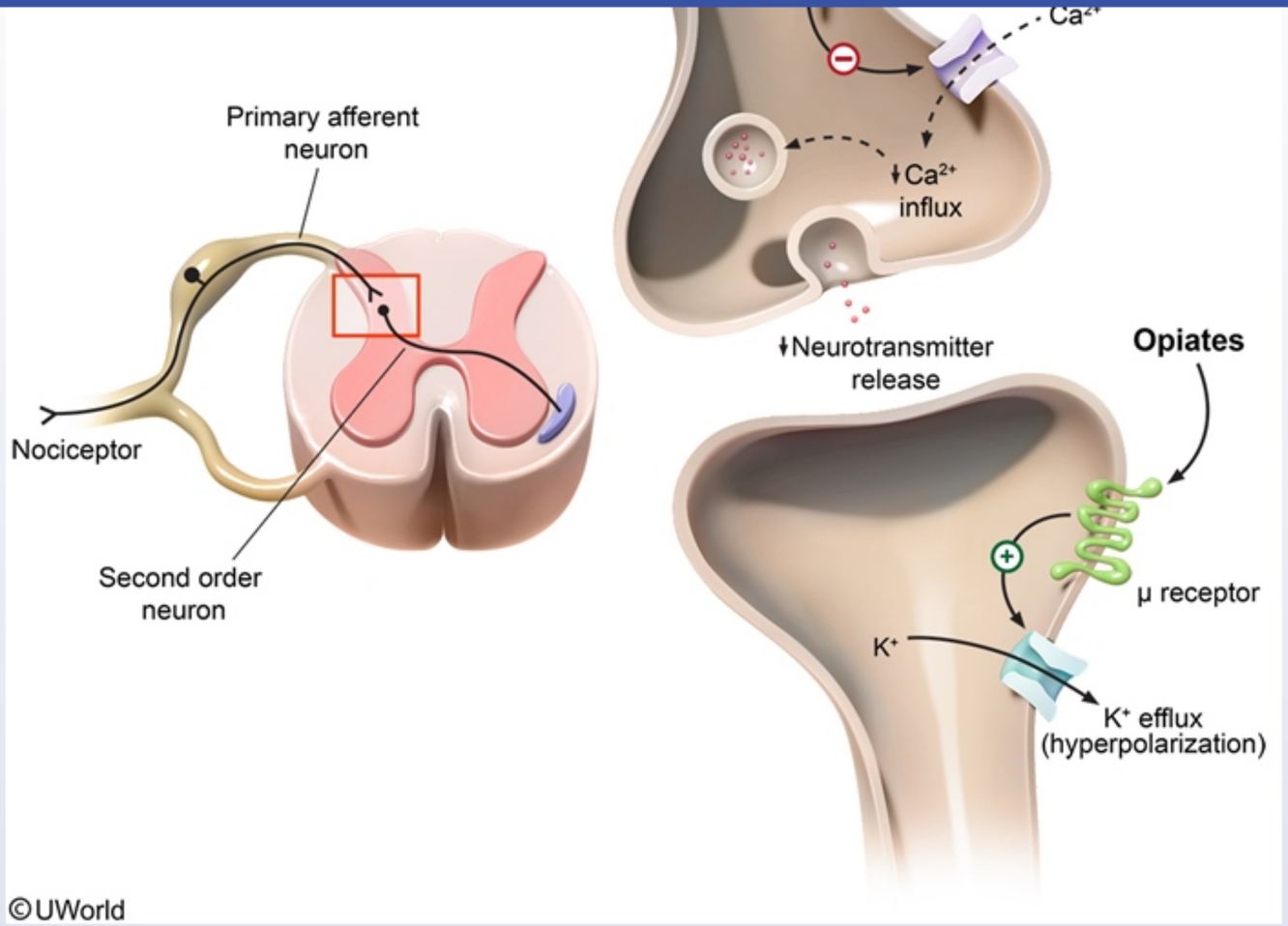

Morphine is an **opiate analgesic** that is commonly used to treat severe chronic pain in patients with cancer. There are 3 main opiate receptor subtypes (eg, mu, delta, kappa) that mediate analgesia at the spinal and supraspinal levels. All of these transmembrane receptors are coupled to inhibitory G proteins. Morphine and other commonly used opiates have an especially high affinity for the **mu receptor**, which exerts the strongest analgesic effects.

In the spine, opiates bind to mu receptors on the primary afferent neuron, resulting in closure of voltage-gated calcium channels, **reduced calcium**

inhibitory G proteins. Morphine and other commonly used opiates have an especially high affinity for the **mu receptor**, which exerts the strongest analgesic effects.

In the spine, opiates bind to mu receptors on the primary afferent neuron, resulting in closure of voltage-gated calcium channels, **reduced calcium influx**, and decreased excitatory neurotransmitter release (eg, acetylcholine, norepinephrine, serotonin, glutamate, substance P) from the **presynaptic terminal (Choice C)**. Opiates also bind to mu receptors on the **postsynaptic membrane**, which opens potassium channels and leads to membrane hyperpolarization due to **potassium efflux**. Opiate-induced inhibition of synaptic activity in the central nervous system attenuates pain transmission, producing analgesia.

(Choice A) Digoxin is a cardiac glycoside that inhibits the sodium-potassium ATPase pump in myocardial cells, resulting in a mild increase in intracellular sodium and indirect inhibition of the sodium-calcium exchanger. This leads to increased intracellular calcium and cardiac contractility, which can help reduce symptoms in patients with advanced systolic heart failure.

(Choice B) Local anesthetics (eg, lidocaine) reduce pain transmission by blocking voltage-dependent sodium channels, which decreases sodium influx and action potential propagation. They are typically used for minor surgical procedures and spinal anesthesia.

(Choice D) Benzodiazepines are sedative-hypnotics that may be indicated for anxiety, panic attacks, or insomnia. They work by increasing chloride influx at GABA-A receptors in the thalamus, limbic structures, and cerebral cortex.

Educational objective:
Opiate analgesics reduce pain by binding to mu receptors and inhibiting synaptic activity in the central nervous system. Activation of presynaptic mu receptors on the primary afferent neuron leads to closure of voltage-gated calcium channels and reduced excitatory neurotransmitter release. Binding to mu receptors on the postsynaptic membrane causes opening of potassium channels and membrane hyperpolarization.

References

- Molecular mechanisms of opioid receptor-dependent signaling and behavior.

Pharmacology	Nervous System	Opioids
Subject	System	Topic

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A 24-year-old previously healthy man is brought to the emergency department after a motor vehicle collision in which he sustained trauma to the left side of the chest and the abdomen. On arrival, the patient is hypotensive and tachycardic. Evaluation reveals left-sided rib fractures and hemoperitoneum due to splenic laceration. Urgent exploratory laparotomy under general anesthesia is planned. In the operating room, etomidate is administered for rapid sequence induction. Which of the following characteristics best describes etomidate as compared to propofol?

A. Analgesic effect in addition to sedation

B. Higher risk of lipid abnormalities

C. Lower risk of adrenocortical suppression

D. No cardiovascular depressant effect

E. Possible use for maintenance anesthesia

Submit

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- A. Analgesic effect in addition to sedation (10%)
- B. Higher risk of lipid abnormalities (3%)
- C. Lower risk of adrenocortical suppression (5%)
- ✓ D. No cardiovascular depressant effect (68%)
- E. Possible use for maintenance anesthesia (12%)

Omitted
Correct answer
D

68%
Answered correctly

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Time Spent

03/31/2020
Last Updated

Explanation

This patient is hemodynamically unstable (ie, hypotensive, tachycardic). Prior to operative intervention, anesthesia must be induced. Three medications are commonly used because of their rapid onset of action and short duration of effect:

- **Propofol:** A highly lipophilic GABA agonist that has the advantage of reducing airway resistance. Disadvantages include **vasodilation**, which can result in hypotension and an increase in serum triglycerides and lipase **(Choice B)**.
- **Etomidate:** A GABA agonist that has the advantage of being the most **hemodynamically neutral**. It does not cause changes in heart rate, blood pressure, or cardiac output. However, it inhibits cortisol synthesis, which can lead to **adrenocortical suppression** that is typically

Explanation

This patient is hemodynamically unstable (ie, hypotensive, tachycardic). Prior to operative intervention, anesthesia must be induced. Three medications are commonly used because of their rapid onset of action and short duration of effect:

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- **Etomidate:** A GABA agonist that has the advantage of being the most **hemodynamically neutral**. It does not cause changes in heart rate, blood pressure, or cardiac output. However, it inhibits cortisol synthesis, which can lead to **adrenocortical suppression** that is typically reversible. Because of this, etomidate is often avoided in patients with septic shock, and it should not be used as maintenance of sedation after induction **(Choices C and E)**.
- **Ketamine:** An N-methyl-d-aspartate antagonist that is similar to PCP, it preserves the respiratory drive during induction of anesthesia. Ketamine also provides an **analgesic effect**. It stimulates the release of catecholamines, which can cause **bronchodilation** but also increase heart rate, myocardial contractility, and cerebral blood flow.

In **hypotensive patients**, anesthesia is often induced with either a hemodynamically neutral agent (**etomidate**) or one that may improve hemodynamics due to catecholamine release (**ketamine**).

(Choice A) In contrast to ketamine, neither propofol nor etomidate provide an analgesic effect.

Educational objective:
Etomidate, a GABA agonist, is often used for anesthesia induction to provide sedation and amnesia. It is hemodynamically neutral, but it can result in transient adrenocortical suppression because it inhibits cortisol synthesis.

Pharmacology	Nervous System	Anesthesia
Subject	System	Topic

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A 5-year-old boy is brought to the emergency department due to accidental drug ingestion. His mother states the patient was playing by himself earlier today and 2 hours later she found him unresponsive in the bathroom. There was an empty bottle of hydrocodone-acetaminophen next to him, but she does not know how many pills were in it. The emergency medical team found the patient stuporous and with bradypnea. His mental status and respirations promptly improved after 1 dose of intravenous naloxone was administered, and he was transported to the hospital. On arrival, the patient is sleepy but arouses easily to voice and follows simple instructions. Vital signs, including respirations, are normal. One hour later, he has worsening lethargy, bradypnea, and miosis. Which of the following most likely accounts for this patient's current clinical deterioration?

A. Acetaminophen-induced liver failure

B. Coingestion of benzodiazepine

C. Incomplete CNS penetrance of naloxone

D. Partial agonistic effect of naloxone

E. Short half-life of naloxone

Submit

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A. Acetaminophen-induced liver failure (9%)

B. Coingestion of benzodiazepine (1%)

C. Incomplete CNS penetrance of naloxone (3%)

D. Partial agonistic effect of naloxone (6%)

✓ E. Short half-life of naloxone (78%)

Omitted
Correct answer
E

78%
Answered correctly

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Time Spent

03/04/2020
Last Updated

Explanation

Clinical features of acute opioid intoxication	
Risk factors	• Substance abuse • Chronic opioid use

Clinical features of acute opioid intoxication	
Risk factors	• Substance abuse • Chronic opioid use • Hospitalized patients (especially postoperative) • Hepatic or renal insufficiency
Clinical findings	• Somnolence, AMS • Pinpoint pupils (miosis) • Shallow breathing & ↓ respiratory rate • Bradycardia, hypothermia, ↓ bowel sounds • Respiratory acidosis on ABG
Management	• Naloxone (may need repeated dosings) • Airway management & ventilation • Exclude other AMS causes (eg, hypoglycemia)

ABG = arterial blood gas; **AMS** = altered mental status.

This young boy, who was found with an empty bottle of hydrocodone-acetaminophen, has evidence of an acute opioid overdose. Opioids (eg, hydrocodone, methadone) exert their analgesic effect via multiple opioid receptors (eg, delta, kappa, mu) in the central and peripheral nervous systems. Typical features of overdose include **decreased level of consciousness, reduced respiratory rate**, decreased bowel sounds, and **miosis**.

Naloxone, a short-acting **opioid antagonist**, is the primary treatment for acute opioid toxicity and rapidly reverses respiratory depression. However, it has a **short half-life** (<1 hr), and most opioids take significantly longer to metabolize (eg, half-life of hydrocodone is 4-8 hrs). Therefore, patients may develop **recurrent symptoms** of opioid toxicity after naloxone is metabolized, and frequent redosing may be necessary.

(Choice A) Acetaminophen poisoning typically causes nausea, vomiting, and malaise in the first 24 hours after ingestion. Liver failure occurs later, and patients typically have jaundice, tachypnea, and confusion (ie, hepatic encephalopathy) that may progress to coma. Bradypnea and

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(Choice A) Acetaminophen poisoning typically causes nausea, vomiting, and malaise in the first 24 hours after ingestion. Liver failure occurs later, and patients typically have jaundice, tachypnea, and confusion (ie, hepatic encephalopathy) that may progress to coma. Bradypnea and miosis are more consistent with opioid toxicity.

(Choice B) Although benzodiazepines cause sedation and respiratory depression, miosis does not occur. In addition, benzodiazepine toxicity is treated with flumazenil, and symptoms would not be expected to improve with naloxone.

(Choice C) Naloxone has excellent CNS penetrance, and this patient's temporary improvement in respiratory rate and somnolence suggests adequate CNS effect. Opioid medications that do not cross the CNS (eg, loperamide) have effects mainly on the gastrointestinal tract and are used to treat diarrhea.

(Choice D) Naloxone is a pure opioid antagonist; it does not have partial agonist activity. Buprenorphine is a partial opioid agonist used to prevent opioid withdrawal while reducing the risk of opioid intoxication (eg, euphoria, respiratory depression).

Educational objective:
Naloxone is a short-acting opioid antagonist used for the treatment of opioid overdose (eg, respiratory depression, decreased level of consciousness, miosis, decreased bowel sounds). Naloxone frequently requires redosing to prevent recurrent overdose symptoms due to its short half-life (<1 hr).

Pharmacology	Nervous System	Opioids
Subject	System	Topic

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A 27-year-old woman comes to the office due to severe, unilateral, throbbing headaches that occur several times a month. The headaches are associated with photophobia, nausea, and occasional vomiting. Over-the-counter analgesics do not provide significant symptom relief. Her mother has a history of similar headaches. Vital signs are within normal limits. Physical examination reveals no abnormalities. A medication is prescribed to treat her condition and the patient is instructed to take it immediately at the onset of a headache. This medication most likely decreases the severity and duration of this patient's headache through which of the following mechanisms?

A. Blockade of dopamine receptors in mesolimbic tract

B. Blockade of serotonin reuptake in cortico-amygdala circuitry

C. Increased availability of acetylcholine in cortical synapses

D. Stimulation of periaqueductal gray area mu receptors

E. Stimulation of trigeminovascular serotonin receptors

Submit

A 27-year-old woman comes to the office due to severe, unilateral, throbbing headaches that occur several times a month. The headaches are associated with photophobia, nausea, and occasional vomiting. Over-the-counter analgesics do not provide significant symptom relief. Her mother has a history of similar headaches. Vital signs are within normal limits. Physical examination reveals no abnormalities. A medication is prescribed to treat her condition and the patient is instructed to take it immediately at the onset of a headache. This medication most likely decreases the severity and duration of this patient's headache through which of the following mechanisms?

A. Blockade of dopamine receptors in mesolimbic tract (4%)

B. Blockade of serotonin reuptake in cortico-amygdala circuitry (16%)

C. Increased availability of acetylcholine in cortical synapses (2%)

D. Stimulation of periaqueductal gray area mu receptors (5%)

✓ E. Stimulation of trigeminovascular serotonin receptors (71%)

Omitted
Correct answer
E

71%
Answered correctly

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Time Spent

03/23/2020
Last Updated

Explanation

Migraines are recurrent, debilitating, unilateral headaches with a pulsating or throbbing quality lasting between 4-72 hours, often with photophobia, phonophobia, and nausea. They can be associated with an aura and are more common in younger women.

Although the pathogenesis of migraines is multifactorial and not fully understood, it is associated with cortical spreading depression (ie, self-propagating neurotransmission across the cortex). Subsequent stimulation of **trigeminal afferents** in the meninges causes the release of

Migraines are recurrent, debilitating, unilateral headaches with a pulsating or throbbing quality lasting between 4-72 hours, often with photophobia, phonophobia, and nausea. They can be associated with an aura and are more common in younger women.

Although the pathogenesis of migraines is multifactorial and not fully understood, it is associated with cortical spreading depression (ie, self-propagating neurotransmission across the cortex). Subsequent stimulation of **trigeminal afferents** in the meninges causes the release of **vasoactive neuropeptides**, including substance P and **calcitonin gene–related peptide** (CGRP), leading to neurogenic inflammation, vasodilation, and plasma protein extravasation. These substances may also contribute to the increased sensitivity of nociceptive pathways to stimuli (ie, neuronal sensitization).

Triptans (eg, sumatriptan) are serotonin **5-hydroxytryptamine 1B/1D agonists** that directly counter migraine headaches by binding to trigeminal serotonin receptors and **inhibiting CGRP** release from the trigeminal neurons. In addition, triptans bind serotonin receptors on the smooth muscle cells of blood vessels, resulting in intracranial vasoconstriction. Triptans are commonly prescribed as **abortive therapy** for acute migraines, particularly in patients who are not responsive to analgesics. Significant adverse effects include dizziness, chest tightness, and **hypertension**.

(Choice A) Antipsychotic medications (eg, haloperidol, risperidone) block the dopamine receptors in the mesolimbic tract and are used in schizophrenia or bipolar disorder. They are not indicated in the treatment of migraine.

(Choice B) Selective serotonin reuptake inhibitors (eg, sertraline, citalopram) block serotonin reuptake in cortico-amygdala pathways. These drugs are used to treat depression and anxiety, not to abort migraines.

(Choice C) Acetylcholinesterase inhibitors (eg, rivastigmine, galantamine) increase the availability of acetylcholine at cortical synapses and are indicated in the treatment of dementia (eg, Alzheimer disease).

(Choice D) Opioid medications (eg, morphine, oxycodone) stimulate mu receptors in the periaqueductal gray area, resulting in modulation of pain. Opioids are not indicated in the treatment of migraines because they increase the risk of chronic migraine, carry a risk of dependence, and are less effective than triptans.

Educational objective:
The pathogenesis of migraines is complex and multifactorial but includes neurogenic inflammation, vasodilation, and sensitization of trigeminal afferents in the meninges. Triptans are serotonin 5-hydroxytryptamine 1B/1D agonists that stimulate the trigeminovascular serotonin receptors,

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serotonin receptors and **inhibiting CGRP** release from the trigeminal neurons. In addition, triptans bind serotonin receptors on the smooth muscle cells of blood vessels, resulting in intracranial vasoconstriction. Triptans are commonly prescribed as **abortive therapy** for acute migraines, particularly in patients who are not responsive to analgesics. Significant adverse effects include dizziness, chest tightness, and **hypertension**.

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The pathogenesis of migraines is complex and multifactorial but includes neurogenic inflammation, vasodilation, and sensitization of trigeminal afferents in the meninges. Triptans are serotonin 5-hydroxytryptamine 1B/1D agonists that stimulate the trigeminovascular serotonin receptors, resulting in inhibition of vasoactive peptide release, intracranial vasoconstriction, and decreased pain. They are used as abortive therapy for acute migraine.

References

- Calcitonin gene-related peptide in migraine: intersection of peripheral inflammation and central modulation.

Pharmacology	Nervous System	Migraine
Subject	System	Topic

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A 26-year-old man with a history of excessive daytime sleepiness due to narcolepsy enrolls in a clinical trial evaluating a new stimulant medication. The patient was previously treated with modafinil, but his symptoms did not improve. It is explained to the patient that the new drug works by promoting the release of dopamine and norepinephrine from nerve terminals in the central nervous system. Adverse effects of the drug are due primarily to excess release of norepinephrine from peripheral autonomic nerve terminals. Which of the following autonomic efferents would be most affected by the use of this drug?

A. Parasympathetic output to the bronchi

B. Parasympathetic output to the heart

C. Preganglionic sympathetic output

D. Sympathetic output to adrenal glands

E. Sympathetic output to eccrine sweat glands

F. Sympathetic output to the detrusor muscle

Submit

A 26-year-old man with a history of excessive daytime sleepiness due to narcolepsy enrolls in a clinical trial evaluating a new stimulant medication. The patient was previously treated with modafinil, but his symptoms did not improve. It is explained to the patient that the new drug works by promoting the release of dopamine and norepinephrine from nerve terminals in the central nervous system. Adverse effects of the drug are due primarily to excess release of norepinephrine from peripheral autonomic nerve terminals. Which of the following autonomic efferents would be most affected by the use of this drug?

- A. Parasympathetic output to the bronchi (1%)
- B. Parasympathetic output to the heart (6%)
- C. Preganglionic sympathetic output (12%)
- D. Sympathetic output to adrenal glands (24%)
- E. Sympathetic output to eccrine sweat glands (16%)
- ✓ F. Sympathetic output to the detrusor muscle (39%)

Omitted
Correct answer
F

39%
Answered correctly

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06/05/2020
Last Updated

Explanation

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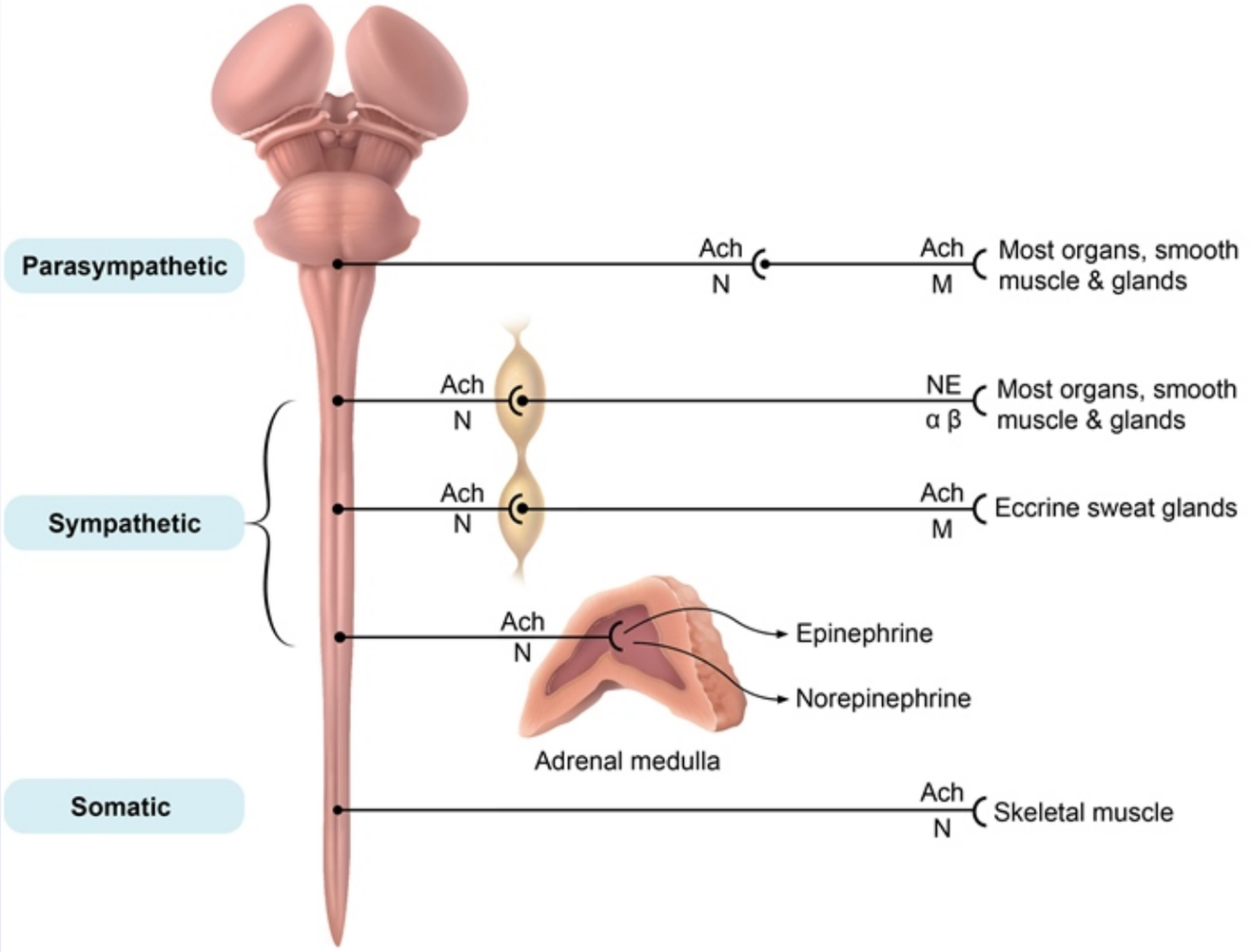
Neurotransmitters



N = nicotinic type; **M** = muscarinic type.
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The parasympathetic and sympathetic subdivisions of the autonomic nervous system regulate most visceral functions of the body via 2-neuron signal transmission. In the parasympathetic system, preganglionic neurons arise from cranial nerve nuclei (eg, CN III, VII, IX, X) and from the

The parasympathetic and sympathetic subdivisions of the autonomic nervous system regulate most visceral functions of the body via 2-neuron signal transmission. In the parasympathetic system, preganglionic neurons arise from cranial nerve nuclei (eg, CN III, VII, IX, X) and from the sacral spinal cord and release acetylcholine, which binds to postganglionic nicotinic receptors found within the parasympathetic ganglia in or near the walls of target organs. Postganglionic neurons also release acetylcholine, activating muscarinic receptors within the target organs (eg, bronchi, heart) **(Choices A and B)**.

In the **sympathetic** system, preganglionic neurons arise from the thoracolumbar spinal cord and release acetylcholine, which binds to postganglionic nicotinic receptors in the sympathetic chain and prevertebral ganglia **(Choice C)**. **Postganglionic** neurons then release **norepinephrine**, activating alpha/beta receptors within target organs (including the bladder); however, there are 2 notable **exceptions** to this scheme:

1. The chromaffin cells of the **adrenal medulla** release norepinephrine and epinephrine directly into the circulation after stimulation by acetylcholine released from sympathetic preganglionic neurons **(Choice D)**.
2. The preganglionic and postganglionic sympathetic neurons that supply eccrine **sweat glands** are both cholinergic **(Choice E)**.

Among the answer choices, only sympathetic output to the detrusor muscle (provided by postganglionic neurons that release norepinephrine) would be significantly affected by the medication. Autonomic output to all the other mentioned structures is mediated by acetylcholine.

Educational objective:
The sympathetic nervous system typically regulates visceral function via 2-neuron signal transmission involving cholinergic preganglionic neurons and adrenergic postganglionic neurons. Eccrine sweat glands and the adrenal medullae are exceptions to this rule as they are both innervated by cholinergic neurons. The parasympathetic system uses both preganglionic and postganglionic cholinergic neurons.

References

- Physiology of the autonomic nervous system.

Pharmacology	Nervous System	Autonomic nervous system
Subject	System	Topic

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A 10-year-old boy is brought to the emergency department due to a fall while riding his bicycle. The patient hit his forehead on a concrete road barrier and sustained a laceration but did not lose consciousness. He reports no headache, nausea, vomiting, vision disturbances, or focal weakness or numbness. The patient received a tetanus vaccine at age 6. Vital signs are within normal limits. Physical examination reveals a 2-cm laceration above the left eyebrow. There are no other injuries. Neurologic examination shows no abnormalities. Prior to laceration repair with suture, lidocaine is injected in the subcutaneous tissue around the laceration. The patient reports immediate relief of pain, and there is loss of sensation to touch in the area infiltrated with the medication. These effects are most likely due to which of the following changes within the affected neurons?

A. Blockade of potassium channels
B. Blockade of sodium channels
C. Decreased calcium current
D. Increased chloride conductance
E. Interruption of axonal transport

Submit

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- A. Blockade of potassium channels (2%)
- ✓ B. Blockade of sodium channels (91%)
- C. Decreased calcium current (2%)
- D. Increased chloride conductance (2%)
- E. Interruption of axonal transport (1%)

Omitted
Correct answer
B

91%
Answered correctly

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03/31/2020
Last Updated

Explanation

Local anesthetic mechanism of action

Extracellular space

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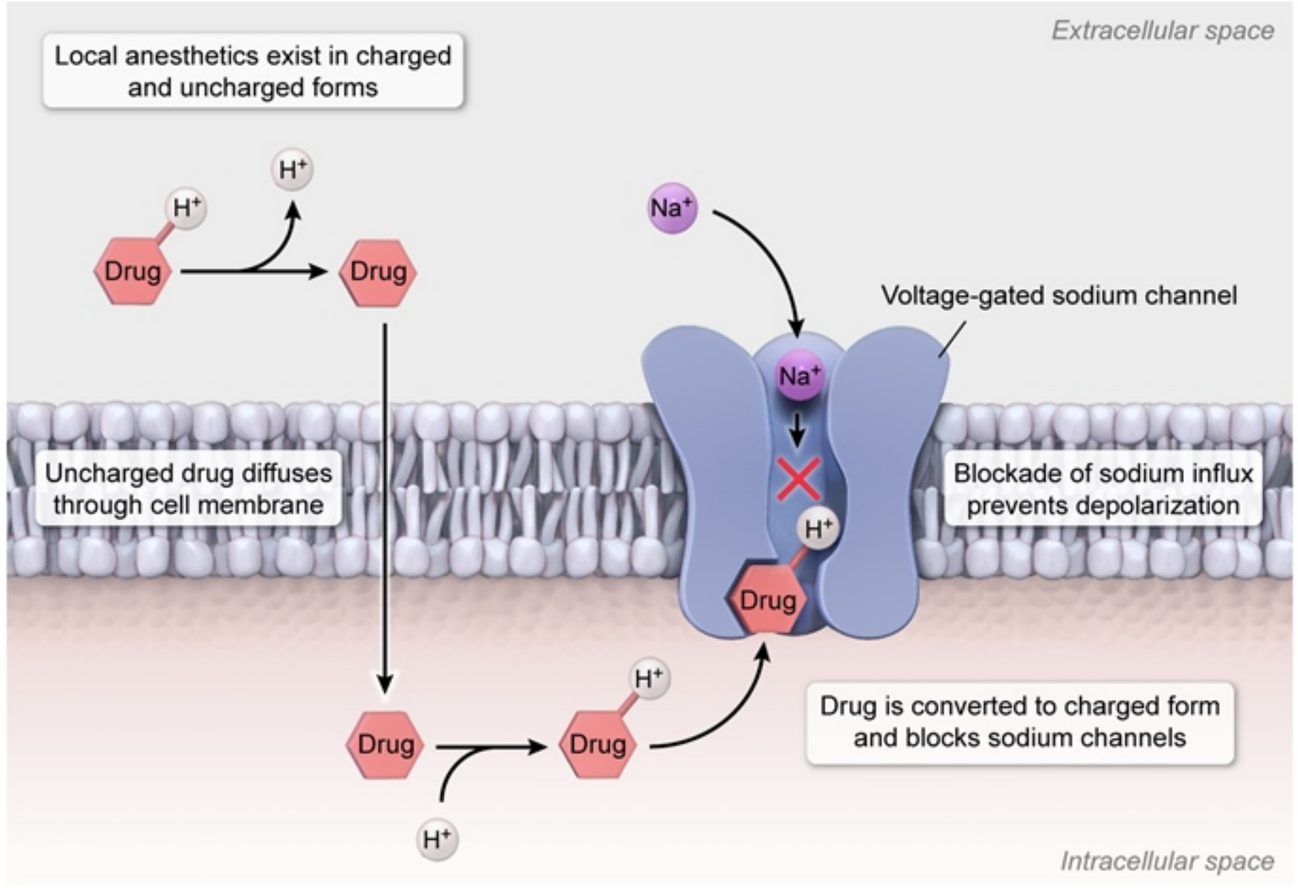
Local anesthetic mechanism of action



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Lidocaine is a **local anesthetic** that interrupts nerve fiber transmission by **blocking sodium channels** in the neuronal cell membrane, preventing depolarization of the nerve. Local anesthetics have a greater effect on **small myelinated nerves**, so they preferentially inhibit neurons that carry pain and temperature sensation; pressure sensation and motor function are often preserved at typical doses.

Lidocaine is a **local anesthetic** that interrupts nerve fiber transmission by **blocking sodium channels** in the neuronal cell membrane, preventing depolarization of the nerve. Local anesthetics have a greater effect on **small myelinated nerves**, so they preferentially inhibit neurons that carry pain and temperature sensation; pressure sensation and motor function are often preserved at typical doses.

Local anesthetics are **weak bases** that exist in charged and uncharged forms. When in the **uncharged form**, they diffuse through the cell membrane to block sodium channels from the inside of the cell. Increased acidity in the surrounding tissue, which occurs in infected wounds, results in more anesthetic molecules remaining in the charged form, rendering them unable to penetrate the cell membrane to exert an effect. Therefore, the dose required to achieve adequate anesthesia is higher in infected tissue.

(Choice A) Blockade of potassium channels would inhibit repolarization, thereby prolonging action potentials and increasing neurotransmitter release at the neuromuscular junction rather than halting action potential propagation.

(Choice C) Decreased calcium current slows the action potential propagation in cells that rely primarily on voltage-gated calcium channels for depolarization, such as cardiac slow response tissues (eg, sinoatrial and atrioventricular nodes); peripheral nerve depolarization is driven primarily by sodium, rather than calcium, influx.

(Choice D) GABA is the primary inhibitory neurotransmitter in the CNS. Activation of the GABA-A receptor, which is the target of some sedating medications (eg, benzodiazepines), activates voltage-gated chloride channels. The influx of chloride ions causes hyperpolarization, which inhibits action potentials.

(Choice E) Interruption of axonal transport delays the delivery of organelles (eg, mitochondria) and synaptic vesicles to the distal axon, causing impaired nerve impulse propagation. This occurs in some neurodegenerative diseases (eg, sporadic Alzheimer) or as an adverse effect of some chemotherapeutic agents (eg, vincristine).

Educational objective:
Local anesthetics diffuse through the neuronal cell membrane to block the influx of sodium into the cell. This prevents depolarization and inhibits action potential propagation.

References

- Molecular mechanisms of local anesthesia: a review.
- Interactions of local anesthetics with voltage-gated Na+ channels.

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Local anesthetics diffuse through the neuronal cell membrane to block the influx of sodium into the cell. This prevents depolarization and inhibits action potential propagation.

References

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Pharmacology	Nervous System	Anesthesia
Subject	System	Topic

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A 46-year-old man comes to the emergency department due to shortness of breath, cough, and fever. The patient began experiencing mild upper respiratory illness a week ago. He has a history of asthma and was using inhaled bronchodilators more frequently since the onset of respiratory illness. Over the past 2 days, he has had worsening breathlessness, productive cough, and high fever. The patient has no other medical conditions. Temperature is 38.9 C (102 F), blood pressure is 90/60 mm Hg, pulse is 120/min, and respirations are 28/min. On physical examination, the patient appears in severe respiratory distress with intercostal retractions. Lung auscultation reveals bilateral wheezing. Prompt endotracheal intubation for respiratory support is planned. Prior to endotracheal intubation, intravenous ketamine is administered for induction of anesthesia. Which of the following characteristics is the most likely reason for use of this anesthetic agent in this patient?

A. Direct GABA agonism

B. Lower lipid solubility

C. Metabolism by plasma enzymes

D. Neuromuscular blockade effect

E. Sympathomimetic activity

Submit

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A. Direct GABA agonism (9%)
B. Lower lipid solubility (18%)
C. Metabolism by plasma enzymes (3%)
D. Neuromuscular blockade effect (23%)
✓ E. Sympathomimetic activity (44%)

Omitted
Correct answer
E

44%
Answered correctly

02 secs
Time Spent

03/25/2020
Last Updated

Explanation

This hemodynamically unstable patient has severe **bronchospasm** and impending respiratory failure and requires intubation. Prior to intubation, anesthesia must be induced. Three medications are commonly used because of their rapid onset of action and short duration of effect.

- **Propofol:** A highly lipophilic GABA agonist that may be used for **long-term sedation**. Disadvantages include vasodilation, which can result

This hemodynamically unstable patient has severe **bronchospasm** and impending respiratory failure and requires intubation. Prior to intubation, anesthesia must be induced. Three medications are commonly used because of their rapid onset of action and short duration of effect.

- **Propofol:** A highly lipophilic GABA agonist that may be used for **long-term sedation**. Disadvantages include vasodilation, which can result in **hypotension** and an increase in serum triglycerides and lipase.
- **Etomidate:** A GABA agonist that has the advantage of being the most **hemodynamically neutral**. It does not cause changes in heart rate, blood pressure, or cardiac output. However, it inhibits cortisol synthesis, which can lead to (reversible) **adrenocortical suppression**. Because of this, it is often avoided in patients with septic shock, and it should not be used as maintenance of sedation after induction.
- **Ketamine:** An N-methyl-D-aspartate (NMDA) antagonist that is similar to PCP; it **preserves the respiratory drive** during induction of anesthesia. In contrast to propofol and etomidate, it also provides an analgesic effect. Ketamine stimulates the release of catecholamines (ie, **sympathomimetic**), which can cause **bronchodilation** but also increase the heart rate, myocardial contractility, and cerebral blood flow, potentially putting the patient at risk for cardiovascular events or increased intracranial pressure.

In this patient with an acute asthma attack, **ketamine** was likely chosen because it stimulates release of catecholamines that increase sympathomimetic activity and may **improve bronchospasm**.

(Choice A) Propofol and etomidate are both GABA agonists, but ketamine works at the NMDA receptor.

(Choice B) Both ketamine and etomidate are much less lipophilic than propofol.

(Choice C) Both ketamine and etomidate are metabolized primarily by the liver. Propofol is also metabolized by the liver, but the effect is terminated by its redistribution rather than metabolism.

(Choice D) Neuromuscular blockade is often used to facilitate intubation. None of the three commonly used induction anesthetics cause significant neuromuscular blockade, so an additional medication (eg, succinylcholine, rocuronium) is used if needed.

Educational objective:
Ketamine can be used for anesthesia induction. The side effects of increased catecholamine release (eg, bronchodilation) are often exploited in patients with bronchospasm.

Pharmacology Nervous System Anesthesia

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Pharmacology	Nervous System	Anesthesia
Subject	System	Topic

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A 15-year-old boy is brought to the office because of 3 months of sudden, brief jerking movements involving both arms. The episodes usually occur shortly after awakening in the morning and are aggravated by sleep deprivation. The movements are neither suppressible nor preceded by an urge to make a movement. The patient has never lost consciousness and has no known medical conditions. Family history includes a seizure disorder in his uncle. Vital signs are within normal limits. Physical examination shows normal development with no abnormalities. Which of the following is the best initial treatment for this patient?

A. Baclofen
B. Carbamazepine
C. Clonidine
D. Diazepam
E. Propranolol
F. Valproic acid
G. Tetrabenazine

Submit

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- A. Baclofen (6%)
- B. Carbamazepine (23%)
- C. Clonidine (4%)
- D. Diazepam (7%)
- E. Propranolol (5%)
- ✓ F. Valproic acid (47%)
- G. Tetrabenazine (5%)

Omitted
Correct answer
F

47%
Answered correctly

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Time Spent

03/02/2020
Last Updated

Explanation

Seizure type	Description	Preferred anticonvulsants

Seizure type	Description	Preferred anticonvulsants
Focal onset (involves a single cerebral hemisphere at onset)		
Aware	• No loss of consciousness or postictal state • Motor, sensory, autonomic, or cognitive symptoms	• Carbamazepine* • Lamotrigine • Levetiracetam • Phenytoin*
Impaired awareness	• Appears awake but consciousness is altered (eg, blank stare) • Postictal state • May have automatisms (eg, lip smacking)	
Generalized onset (involves both hemispheres at onset)		
Tonic-clonic	• Loss of consciousness & postictal state • Diffuse muscle contraction of limbs (tonic) followed by rhythmic jerking (clonic)	• Levetiracetam • Valproic acid
Myoclonic	• No loss of consciousness or postictal state • Brief jerking movements	
Absence	• Brief episodes of altered consciousness (eg, blank stare) • May have automatisms • Usually no postictal state	• Ethosuxamide • Valproic acid

*Narrow-spectrum agents can also treat focal-onset seizures that evolve into bilateral tonic-clonic seizures.

This patient most likely has **myoclonic seizures** due to juvenile myoclonic epilepsy (JME), a form of **generalized onset epilepsy** (ie, affecting both cerebral hemispheres at onset) that may be familial. Typically, JME manifests in an otherwise healthy adolescent with myoclonic seizures (ie, **brief, involuntary jerking movements**) involving both upper extremities with preservation of consciousness. Symptoms usually occur within the first hour of awakening and can be provoked by sleep deprivation. Patients can also develop tonic-clonic and/or absence seizures.

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Treatment of generalized onset epilepsies like JME should include a **broad-spectrum anticonvulsant** (eg, **valproic acid**, levetiracetam) which can treat both focal and generalized seizures. In contrast, narrow-spectrum anticonvulsants (eg, carbamazepine, phenytoin) are primarily used only in patients with focal onset seizures and can worsen seizure symptoms in patients with absence or myoclonic seizures **(Choice B)**.

(Choice A) Baclofen is a GABA-B agonist that can treat chronic muscle spasticity (eg, cerebral palsy). Patients with chronic muscle spasticity typically have progressive changes in development and muscle tone that would be apparent on physical examination.

(Choice C) Clonidine is an alpha-2 adrenergic receptor agonist that may be effective in children with attention-deficit hyperactivity disorder who have failed treatment with stimulants (eg, methylphenidate).

(Choice D) Diazepam is a benzodiazepine that can be used acutely to treat prolonged seizures such as status epilepticus (≥5 minutes of continuous seizure activity or >1 seizure without recovery in between). However, diazepam would not be indicated for this patient's brief episodes of myoclonus.

(Choice E) Propranolol is a nonselective beta blocker that can treat benign essential tremor, which typically presents in middle-aged adults with bilateral, rhythmic hand tremor that worsens during fine motor activity.

(Choice G) Tetrabenazine is a dopamine depletion agent that can treat Tourette syndrome, a disorder characterized by motor and phonic tics that persist for >1 year. Motor tics can manifest as periodic, sudden, jerking movements, but they are usually temporarily suppressible and often preceded by an urge to make the stereotyped movement.

Educational objective:
Broad-spectrum anticonvulsants (eg, levetiracetam, valproic acid) treat both focal and generalized onset seizures, whereas narrow-spectrum anticonvulsants (eg, carbamazepine, phenytoin) are primarily used only for focal onset seizures. Because the seizures in juvenile myoclonic epilepsy are usually generalized onset (ie, affect both cerebral hemispheres at onset), treatment is with a broad-spectrum agent such as valproic

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References

- Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data.

Pharmacology	Nervous System	Seizures
Subject	System	Topic

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A 42-year-old previously healthy man comes to the office due to an enlarging mole. The patient has had a mole on his forearm for the past several years, and it has rapidly increased in size over the past 4 months. Physical examination shows an 8-mm raised lesion with variegated pigmentation and ill-defined borders on the right forearm. Excisional biopsy of the lesion is planned. Local anesthesia is administered via an infiltrating injection of lidocaine mixed with epinephrine. Which of the following is the most likely impact of mixing the latter medication with the anesthetic agent?

A. Altered neurotransmitter levels of nociceptive fibers

B. Decreased pain during subcutaneous infiltration

C. Increased anesthesia efficacy by synergistic effect

D. Increased anesthesia potency by decreasing tissue pH

E. Prolonged duration of action of the anesthetic agent

Submit

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- A. Altered neurotransmitter levels of nociceptive fibers (4%)
- B. Decreased pain during subcutaneous infiltration (4%)
- C. Increased anesthesia efficacy by synergistic effect (22%)
- D. Increased anesthesia potency by decreasing tissue pH (5%)
- ✓ E. Prolonged duration of action of the anesthetic agent (63%)

Omitted
Correct answer
E

63%
Answered correctly

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Time Spent

03/30/2020
Last Updated

Explanation

Local anesthetic mechanism of action

Extracellular space

Local anesthetics exist in charged and uncharged forms

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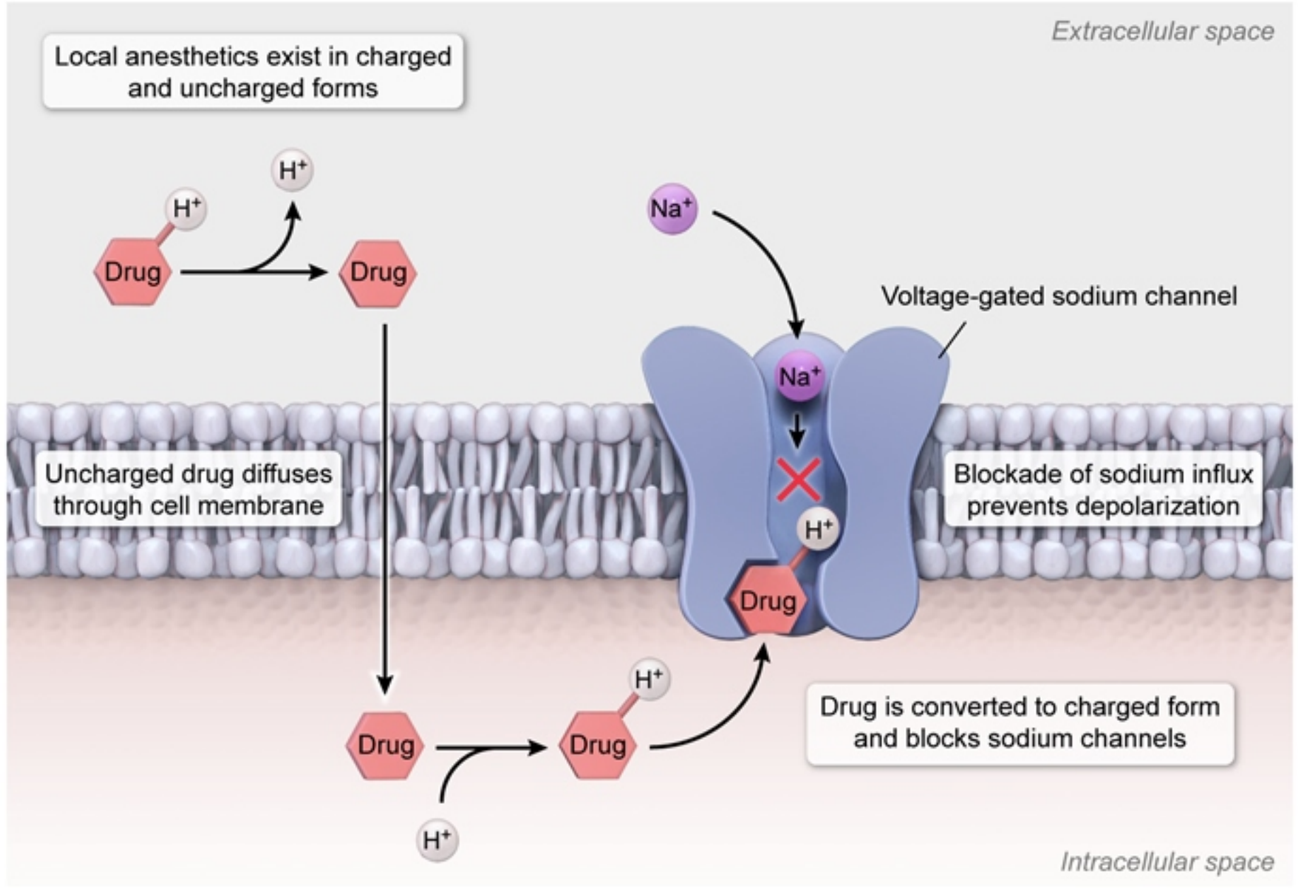
Local anesthetic mechanism of action



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Lidocaine is a **local anesthetic** that blocks transmission from free nerve endings. It is often mixed with epinephrine, which causes **profound vasoconstriction** when injected subcutaneously. This results in the following:

- A decrease in local bleeding, making the procedure easier to complete

Lidocaine is a **local anesthetic** that blocks transmission from free nerve endings. It is often mixed with epinephrine, which causes **profound vasoconstriction** when injected subcutaneously. This results in the following:

- A decrease in local bleeding, making the procedure easier to complete
- **A prolonged duration of action** because more lidocaine remains at the site of injection
- A decrease in systemic absorption, reducing the potential for serious adverse effects (eg, arrhythmias, seizures)

(Choice A) Although epinephrine acts as a catecholamine neurotransmitter in the CNS, it mediates autonomic functions in the peripheral nervous system. Glutamate and substance P are the main neurotransmitters of pain sensation in the peripheral nervous system.

(Choices B and D) Local anesthetics are weak bases that exist in charged and uncharged forms; the uncharged form must diffuse through the cell membrane and bind the inside portion of sodium channels in order to prevent depolarization. Increased acidity in the surrounding tissue results in more anesthetic molecules remaining in the charged form, preventing them from penetrating the cell membrane to exert an effect. Therefore, sodium bicarbonate is often added to lidocaine with epinephrine to increase the pH, which improves potency. This increase in pH also decreases pain at the injection site.

(Choice C) Medications interact synergistically when they produce the same result by different mechanisms (eg, opioids + acetaminophen). Epinephrine does not produce anesthesia, so although it prolongs the duration of anesthesia, it does not act synergistically to increase the anesthetic effect.

Educational objective:
Epinephrine is often added to lidocaine to produce vasoconstriction, which prolongs lidocaine's duration of action, decreases bleeding during the procedure, and reduces systemic lidocaine absorption.

Pharmacology	Nervous System	Anesthesia
Subject	System	Topic

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A 64-year-old man comes to the office due to slowing of his movements and gait instability that has been the cause of several recent falls. The patient was diagnosed with Parkinson disease a year ago. On examination, there is a resting tremor involving the right hand and rigidity during passive flexion and extension of the right upper limb. The patient is started on therapy with pramipexole. Which of the following best describes the mechanism of action of this medication?

A. Decreases central dopamine degradation

B. Directly stimulates dopamine receptors

C. Enhances the effect of endogenous dopamine

D. Increases dopamine precursor availability in the brain

E. Inhibits central muscarinic receptors

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A. Decreases central dopamine degradation (15%)
✓ B. Directly stimulates dopamine receptors (50%)
C. Enhances the effect of endogenous dopamine (14%)
D. Increases dopamine precursor availability in the brain (10%)
E. Inhibits central muscarinic receptors (9%)

Omitted
Correct answer
B

50%
Answered correctly

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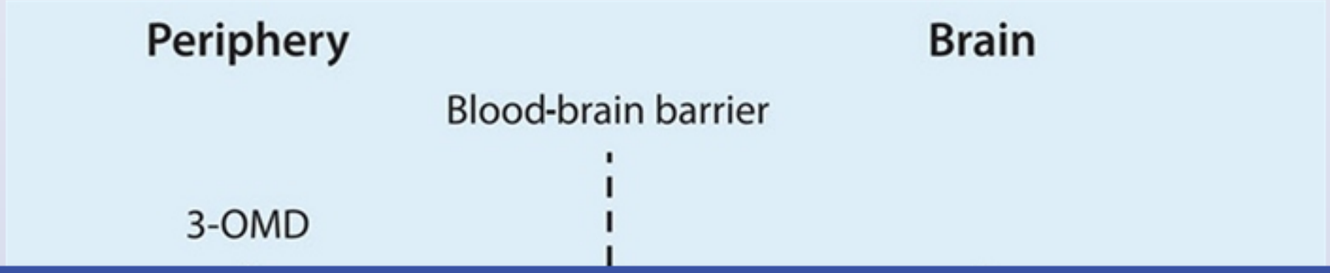
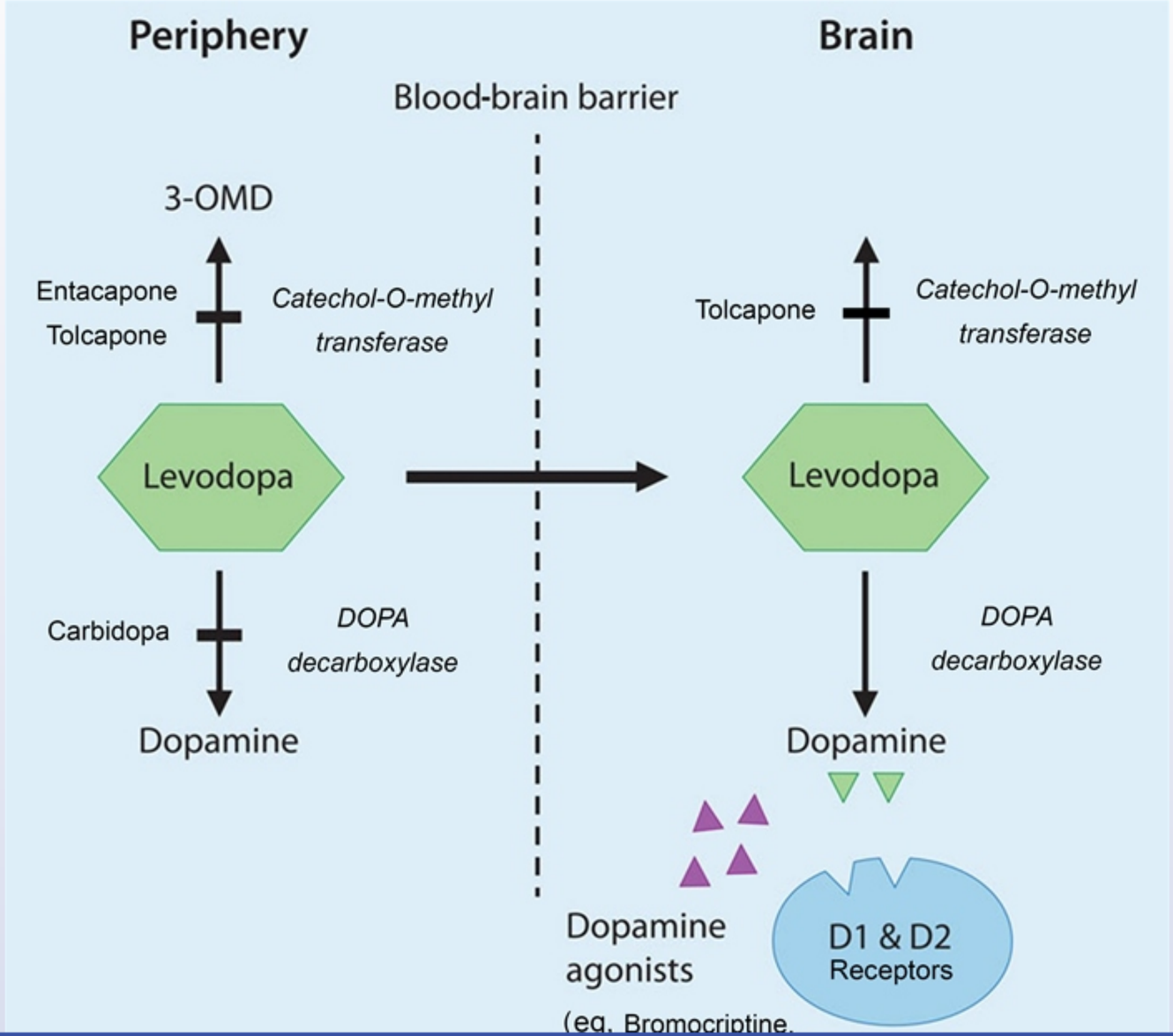
Time Spent

02/09/2020
Last Updated

Explanation




Periphery
Brain
Blood-brain barrier
3-OMD
Entacapone
Tolcapone
Catechol-O-methyl transferase
Levodopa
Carbidopa
DOPA decarboxylase
Dopamine
Tolcapone
Catechol-O-methyl transferase
Levodopa
DOPA decarboxylase
Dopamine
Dopamine agonists
(eg. Bromocriptine,
D1 & D2 Receptors

Dopamine agonists have a chemical structure similar to the neurotransmitter dopamine and directly stimulate dopamine receptors. They do not have to be metabolized to be active. There are 2 classes of dopamine agonists:

- Ergot compounds (derived from ergot fungi): **bromocriptine**
- Nonergot compounds: **pramipexole** and **ropinirole**

Dopamine agonists have an important role in the treatment of **Parkinson disease** (PD) as these medications have a long half-life and can delay the need to start levodopa, thereby postponing the development of motor fluctuations until later in the disease course. Bromocriptine also treats hyperprolactinemia.

(Choice A) Selegiline is used to delay the clinical progression of PD via inhibition of monoamine oxidase-B (MAO-B) in the brain, resulting in decreased central dopamine degradation.

(Choice C) Amantadine exerts several effects with regard to PD. As an indirect and direct dopaminergic agent, it alleviates some of the motor symptoms of PD by enhancing the effects of endogenous dopamine. It is thought also to have some anticholinergic properties, which reduce tremors.

(Choice D) Both catechol-O-methyltransferase (COMT) inhibitors (eg, entacapone, tolcapone) and dopa decarboxylase inhibitors (eg, carbidopa) decrease the breakdown of levodopa in peripheral tissues and increase the amount of levodopa available to cross the blood-brain barrier.

(Choice E) Anticholinergics, such as trihexyphenidyl and benztropine, inhibit central muscarinic receptors. These drugs are sometimes used to treat patients with drug-induced parkinsonism and those with tremor as the predominant symptom of idiopathic PD.

Educational objective:
Dopamine agonists have a chemical structure similar to the neurotransmitter dopamine and directly stimulate dopamine receptors. The 2 classes of dopamine agonists are ergot compounds (eg, bromocriptine) and nonergot compounds (eg, pramipexole, ropinirole).

References

- Current pharmacotherapeutic treatment options in Parkinson's disease.
- Parkinson's disease: diagnosis and treatment.

Pharmacology Nervous System Parkinson disease

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A 54-year-old man is hospitalized after a planned abdominal surgery. One of his physicians administers a new drug whose mechanism of action you do not know. Shortly after administration of the drug the patient develops flushing, diaphoresis and nausea. His blood pressure is 100/70 mmHg and heart rate is 55/min. His pupils are constricted but reactive to light. This medication is most likely given for which of the following conditions?

A. Urinary tract infection

B. Urinary obstruction

C. Atonic bladder

D. Fluid overload

E. Hypovolemic shock

Submit

A 54-year-old man is hospitalized after a planned abdominal surgery. One of his physicians administers a new drug whose mechanism of action you do not know. Shortly after administration of the drug the patient develops flushing, diaphoresis and nausea. His blood pressure is 100/70 mmHg and heart rate is 55/min. His pupils are constricted but reactive to light. This medication is most likely given for which of the following conditions?

- A. Urinary tract infection (3%)
- B. Urinary obstruction (17%)
- ✓ C. Atonic bladder (69%)
- D. Fluid overload (5%)
- E. Hypovolemic shock (5%)

Omitted
Correct answer
C

69%
Answered correctly

01 sec
Time Spent

02/03/2020
Last Updated

Explanation

The patient described in this vignette displays symptoms associated with cholinergic agonists. These medications increase GI tract smooth muscle tone to produce nausea, vomiting, abdominal cramps and diarrhea. Cholinergic agonists decrease heart rate, cardiac conduction and contractility, and may result in bradycardia, partial or complete heart block, and hypotension. Cholinergic-associated peripheral vasodilatation decreases blood pressure due to the stimulation of endothelial nitric oxide synthesis. Cholinergic agonists also increase secretion, leading to excessive sweating, salivation and lacrimation. These drugs can cause dyspnea via bronchoconstriction (increased smooth muscle tone in the tracheobronchial tree) and increased bronchial secretion.

C

Explanation

The patient described in this vignette displays symptoms associated with cholinergic agonists. These medications increase GI tract smooth muscle tone to produce nausea, vomiting, abdominal cramps and diarrhea. Cholinergic agonists decrease heart rate, cardiac conduction and contractility, and may result in bradycardia, partial or complete heart block, and hypotension. Cholinergic-associated peripheral vasodilatation decreases blood pressure due to the stimulation of endothelial nitric oxide synthesis. Cholinergic agonists also increase secretion, leading to excessive sweating, salivation and lacrimation. These drugs can cause dyspnea via bronchoconstriction (increased smooth muscle tone in the tracheobronchial tree) and increased bronchial secretion.

There are several cholinergic agonists used in medicine. Bethanechol is a cholinergic agonist used to stimulate peristalsis in postoperative ileus. This drug is also used to treat non-obstructive urinary retention (atonic bladder). Carbachol and pilocarpine are used to lower intraocular pressure in glaucoma. Cholinergic-associated miosis causes the iris to move further from the cornea. This widens the anterior chamber angle and allows for better outflow of the aqueous humor.

(Choices A and B) Cholinergic agonists are not used to treat urinary tract infections or urinary obstruction.

(Choice D) Clinically evident volume overload is treated with loop diuretics. Cholinergic agents will not help this condition.

(Choice E) Hypovolemic shock is treated with IV fluids. Administering a cholinergic agent would likely worsen hypovolemic shock.

Educational Objective:
Cholinomimetics are indicated in non-obstructive urinary retention, paralytic ileus, and glaucoma. Their side effects include nausea, vomiting, abdominal cramps, diarrhea, dyspnea and increased secretions (sweating, lacrimation and salivation).

Pharmacology	Nervous System	Urinary retention
Subject	System	Topic

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A 21-year-old man is brought to the emergency department by his mother after she found him violently shaking on the kitchen floor of her home. The patient urinated on himself and bit his tongue during the incident. He has a past medical history of posttraumatic epilepsy and is noncompliant with his antiseizure medications. In the hospital, he has several brief, back-to-back generalized tonic-clonic seizures and never fully regains consciousness between episodes. Intravenous lorazepam 2 mg is administered, and the seizures stop. Intravenous infusion of another drug is started simultaneously to prevent seizure recurrence. Which of the following is the most likely mechanism of action of the second drug infused in this patient?

A. Decreases calcium current in thalamic neurons

B. Decreases sodium current in cortical neurons

C. Dose-dependent activation of postsynaptic $GABA_A$ receptors

D. Increases postsynaptic chloride influx

E. Irreversible inhibition of GABA catabolism in the central nervous system

Submit

A 21-year-old man is brought to the emergency department by his mother after she found him violently shaking on the kitchen floor of her home. The patient urinated on himself and bit his tongue during the incident. He has a past medical history of posttraumatic epilepsy and is noncompliant with his antiseizure medications. In the hospital, he has several brief, back-to-back generalized tonic-clonic seizures and never fully regains consciousness between episodes. Intravenous lorazepam 2 mg is administered, and the seizures stop. Intravenous infusion of another drug is started simultaneously to prevent seizure recurrence. Which of the following is the most likely mechanism of action of the second drug infused in this patient?

- A. Decreases calcium current in thalamic neurons (5%)
- ✓ B. Decreases sodium current in cortical neurons (66%)
- C. Dose-dependent activation of postsynaptic $GABA_A$ receptors (12%)
- D. Increases postsynaptic chloride influx (10%)
- E. Irreversible inhibition of GABA catabolism in the central nervous system (4%)

Omitted
Correct answer
B

66%
Answered correctly

01 sec
Time Spent

05/19/2020
Last Updated

Explanation

Mechanisms of common antiseizure drugs	
Phenytoin	Blocks Na^+ channels
Carbamazepine	

Mechanisms of common antiseizure drugs	
Phenytoin	Blocks Na^+ channels
Carbamazepine	
Valproic acid	Blocks Na^+ channels & ↑ GABA levels
Benzodiazepine	↑ $GABA_A$ action
Phenobarbital	
Levetiracetam	Modulates GABA & glutamate release
Ethosuximide	Blocks thalamic T-type Ca^{2+} channels

Status epilepticus is a single seizure lasting >5 minutes or the occurrence of multiple discrete seizures with incomplete recovery of consciousness between episodes. Common causes include structural brain injury (eg, stroke, tumor, head trauma), infection, metabolic abnormalities (eg, hypoglycemia), and medication noncompliance in individuals with known epilepsy. Prompt evaluation and treatment is necessary as the condition is life-threatening and associated with a number of systemic complications (eg, cardiac arrhythmias, hypoventilation/hypoxia, disabling neurologic deficits).

Intravenous **lorazepam** is a benzodiazepine that potentiates the effects of the inhibitory neurotransmitter GABA in the central nervous system. It is the initial drug of choice for treatment of status epilepticus due to its efficacy and rapid onset of action. Intravenous **phenytoin** (or fosphenytoin) is a long-acting anticonvulsant that is administered **concurrently** to prevent the recurrence of seizure activity, regardless of patient responsiveness to lorazepam. Phenytoin inhibits neuronal high-frequency firing in the cortex by reducing the ability of **sodium channels** to recover from inactivation.

(Choice A) Ethosuximide blocks T-type calcium channels in thalamic neurons. It is a first-line treatment for absence seizures.

(Choices C and D) Benzodiazepines and barbiturates (eg, phenobarbital) bind to the ligand-gated chloride channel of the $GABA_A$ receptor. These substances enhance the inhibitory effect of GABA by increasing postsynaptic chloride influx.

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(Choices C and D) Benzodiazepines and barbiturates (eg, phenobarbital) bind to the ligand-gated chloride channel of the $GABA_A$ receptor. These substances enhance the inhibitory effect of GABA by increasing postsynaptic chloride influx.

(Choice E) Vigabatrin is an irreversible inhibitor of GABA transaminase, the enzyme responsible for GABA catabolism in the central nervous system. Vigabatrin is one of several drugs that can be used in cases of treatment-resistant epilepsy.

Educational objective:
Status epilepticus is a single seizure lasting >5 minutes or the occurrence of multiple discrete seizures with incomplete recovery of consciousness between episodes. The initial treatment includes intravenous lorazepam and phenytoin given concurrently. Phenytoin is a long-acting anticonvulsant that inhibits neuronal high-frequency firing by reducing the ability of sodium channels to recover from inactivation.

References

- The management of status epilepticus.
- Basis of the antiseizure action of phenytoin.

Pharmacology	Nervous System	Seizures
Subject	System	Topic

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A new inhaled anesthetic under development by a pharmaceutical company is tested in a series of experiments to determine its pharmacokinetic properties. During one of the experiments, the anesthetic agent is administered at a constant partial pressure while arterial and venous concentrations are monitored. The study results show that the anesthetic has a very large arteriovenous concentration gradient shortly after beginning inhalation. Which of the following best describes the properties of the new anesthetic?

A. Fast equilibration with the brain
B. Low peripheral tissue solubility
C. Low peripheral tissue uptake
D. Low potency
E. Slow onset of action

Submit

A new inhaled anesthetic under development by a pharmaceutical company is tested in a series of experiments to determine its pharmacokinetic properties. During one of the experiments, the anesthetic agent is administered at a constant partial pressure while arterial and venous concentrations are monitored. The study results show that the anesthetic has a very large arteriovenous concentration gradient shortly after beginning inhalation. Which of the following best describes the properties of the new anesthetic?

- A. Fast equilibration with the brain (35%)
- B. Low peripheral tissue solubility (14%)
- C. Low peripheral tissue uptake (11%)
- D. Low potency (10%)
- ✓ E. Slow onset of action (28%)

Omitted
Correct answer
E

28%
Answered correctly

01 sec
Time Spent

01/16/2020
Last Updated

Explanation

Before gas anesthetics can reach the target organ (brain), they must move through a number of compartments (inhaled air → lungs → blood→ brain). The onset of anesthesia occurs when a sufficient quantity of anesthetic is transferred to the brain. The factors shown in the table influence the rate of transfer of anesthetic through the compartments and determine the onset of action.

Factors influencing anesthetic concentration		

Before gas anesthetics can reach the target organ (brain), they must move through a number of compartments (inhaled air → lungs → blood→ brain). The onset of anesthesia occurs when a sufficient quantity of anesthetic is transferred to the brain. The factors shown in the table influence the rate of transfer of anesthetic through the compartments and determine the onset of action.

Factors influencing anesthetic concentration

Compartment	Determinants of anesthetic concentration	Effect
Inhaled air	The partial pressure (ie, tension) of the anesthetic in the inspired gas	Anesthetic tension throughout the body will eventually equilibrate with its tension in the inspired air. When this occurs, the tissues are said to become saturated.
Lungs	Pulmonary ventilation rate	The rate of rise of gas tension in alveoli is directly proportional to both the rate & depth of respiration.
Blood	Solubility of the anesthetic in the blood (blood/gas partition coefficient)	Higher blood solubility means that more anesthetic must be absorbed by the blood before it can be effectively transferred to other tissues.
Target organ	Solubility of the anesthetic in the peripheral tissues negatively	Higher peripheral tissue solubility means more anesthetic is extracted from the arterial blood. This increases the arteriovenous concentration gradient,

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Factors influencing anesthetic concentration

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Blood	Solubility of the anesthetic in the blood (blood/gas partition coefficient)	Higher blood solubility means that more anesthetic must be absorbed by the blood before it can be effectively transferred to other tissues.
Target organ (brain)	Solubility of the anesthetic in the peripheral tissues negatively affects brain saturation.	Higher peripheral tissue solubility means more anesthetic is extracted from the arterial blood. This increases the arteriovenous concentration gradient, meaning that more anesthetic must be absorbed to saturate the blood & then the brain.

Inhaled air	of the anesthetic in the inspired gas	in the inspired air. When this occurs, the tissues are said to become saturated.
Lungs	Pulmonary ventilation rate	The rate of rise of gas tension in alveoli is directly proportional to both the rate & depth of respiration.
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The arteriovenous concentration gradient is the difference between the concentration of a gas anesthetic in arterial and venous blood. The solubility of the anesthetic in the peripheral tissues is a major factor in determining the size of the arteriovenous gradient. If tissue solubility is high, a large amount of anesthetic is taken up from arterial blood, which results in low venous concentration. As a result, saturation of the blood requires further absorption of anesthetic in order to replace that which is absorbed by the peripheral tissues. Because blood saturation takes longer, brain saturation is also delayed and onset of action is slower.

In contrast, anesthetic gases with low peripheral tissue solubility have smaller arteriovenous gradients as there is less peripheral tissue uptake **(Choices B and C)**. Less anesthetic is required to replace the amount absorbed by the peripheral tissue and so blood saturation occurs quickly.

Target organ (brain)	Solubility of the anesthetic in the peripheral tissues negatively affects brain saturation.	arterial blood. This increases the arteriovenous concentration gradient, meaning that more anesthetic must be absorbed to saturate the blood & then the brain.

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The arteriovenous concentration gradient is the difference between the concentration of a gas anesthetic in arterial and venous blood. The solubility of the anesthetic in the peripheral tissues is a major factor in determining the size of the arteriovenous gradient. If tissue solubility is high, a large amount of anesthetic is taken up from arterial blood, which results in low venous concentration. As a result, saturation of the blood requires further absorption of anesthetic in order to replace that which is absorbed by the peripheral tissues. Because blood saturation takes longer, brain saturation is also delayed and onset of action is slower.

In contrast, anesthetic gases with low peripheral tissue solubility have smaller arteriovenous gradients as there is less peripheral tissue uptake **(Choices B and C)**. Less anesthetic is required to replace the amount absorbed by the peripheral tissue and so blood saturation occurs quickly, allowing concentrations in the brain to equilibrate faster **(Choice A)**.

(Choice D) Potency of the anesthetic is defined by the minimal alveolar concentration (MAC), the alveolar concentration that prevents movement in 50% of patients exposed to noxious stimuli. Potent anesthetics have low MACs. The arteriovenous concentration gradient influences the rate of induction, not anesthetic potency.

Educational objective:
The arteriovenous concentration gradient reflects the overall tissue solubility of an anesthetic. Anesthetics with high tissue solubility are characterized by large arteriovenous concentration gradients and slower onsets of action.

Pharmacology	Nervous System	Anesthesia
Subject	System	Topic

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MPTP is a toxic substance that induces a Parkinsonism-like syndrome by destroying dopaminergic neurons in the CNS. A series of experiments demonstrated that MPTP per se is minimally toxic. Actually, it is a metabolite of MPTP, produced by MAO type B and called MPP+, that causes the neurological damage. Pretreatment by which of the following agents would minimize the damage induced by MPTP consumption?

A. Amantadine
B. Levodopa
C. Levodopa/carbidopa
D. Selegiline
E. Pergolide

Submit

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- A. Amantadine (5%)
- B. Levodopa (2%)
- C. Levodopa/carbidopa (9%)
- ✓ D. Selegiline (79%)
- E. Pergolide (3%)

Omitted
Correct answer
D

79%
Answered correctly

01 sec
Time Spent

01/13/2020
Last Updated

Explanation

Selegiline is an inhibitor of MAO, type B. Since the actual causative agent of MPTP-associated Parkinsonism-type symptoms is formed by MAO, type B, pretreatment with selegiline can prevent this damage to dopaminergic neurons. Clinically, selegiline is used to delay the progression of Parkinson disease.

(Choice A) Amantadine was designed as an antiviral influenza agent, but it is also known to have dopaminergic activity and possibly anticholinergic action as well; therefore, it may provide moderate improvement in patients with Parkinson disease. Amantadine and anticholinergic agents may produce undesirable side effects such as dry mouth, nausea, vomiting, blurring of vision, visual hallucinations, and other mental

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(Choice B) Dopamine is absent in the nigrostriatum of patients with Parkinson disease. Dopamine itself cannot be directly administered because it is unable to cross the blood-brain barrier. Levodopa, or L-dopa, is the immediate precursor of dopamine. It is taken up by the brain, engulfed in the striatum by cell processes that have cell bodies in the substantia nigra; then, in the substantia nigra, L-dopa is converted to dopamine, and released as a neurotransmitter.

(Choice C) Levodopa is a dopamine analog that remains the most effective treatment for symptoms of Parkinson disease. Levodopa is absorbed in the small intestine via a large, neutral-amino-acid transporter system and is then converted to dopamine by the enzyme dopa-decarboxylase. Peripheral conversion to dopamine is largely responsible for the nausea and vomiting associated with L-dopa use. The addition of dopa-decarboxylase inhibitors (carbidopa) that do not cross the blood-brain barrier decrease the peripheral formation of dopamine, relieving the intense nausea and vomiting caused by levodopa alone.

(Choice E) Pergolide is a dopamine agonist which directly stimulates dopamine D2 receptors. It provides only modest improvement in parkinsonian symptoms when used as monotherapy; however, this modest improvement may be sufficient to delay the introduction of levodopa by months or years, thus delaying levodopa-related side effects.

Educational Objective:

1. Selegiline is an inhibitor of MAO, type B and can prevent MPTP-induced damage of dopaminergic neurons.
2. Selegiline is used clinically to delay the progression of Parkinson disease.
3. Many neurologists favor the use of combinations of selegiline, anticholinergics, and amantadine until they no longer provide control of symptoms. Only then is levodopa/carbidopa introduced.

anticholinergic action as well; therefore, it may provide moderate improvement in patients with Parkinson disease. Amantadine and anticholinergic agents may produce undesirable side effects such as dry mouth, nausea, vomiting, blurring of vision, visual hallucinations, and other mental changes; they should be used with caution in the elderly.

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Educational Objective:

1. Selegiline is an inhibitor of MAO, type B and can prevent MPTP-induced damage of dopaminergic neurons.
2. Selegiline is used clinically to delay the progression of Parkinson disease.
3. Many neurologists favor the use of combinations of selegiline, anticholinergics, and amantadine until they no longer provide control of symptoms. Only then is levodopa/carbidopa introduced.

Pharmacology	Nervous System	Parkinson disease
Subject	System	Topic

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A 30-year-old man comes to the emergency department with sudden onset of severe headache and confusion. He has a history of autosomal dominant polycystic kidney disease. Neurological examination shows no meningeal signs or focal neurological deficits. CT scan of the head reveals blood in the subarachnoid space. The patient is admitted to the critical care unit for further management. On the fifth day after admission, he experiences new-onset weakness in the right arm and leg. Which of the following medications could have most likely prevented the neurological complications this patient developed in the hospital?

- A. ACE inhibitor
- B. Beta-adrenergic blocker
- C. Calcium channel blocker
- D. Central sympatholytic
- E. Nitrate
- F. Osmotic diuretic
- G. Thiazide diuretic

Submit

A 30-year-old man comes to the emergency department with sudden onset of severe headache and confusion. He has a history of autosomal dominant polycystic kidney disease. Neurological examination shows no meningeal signs or focal neurological deficits. CT scan of the head reveals blood in the subarachnoid space. The patient is admitted to the critical care unit for further management. On the fifth day after admission, he experiences new-onset weakness in the right arm and leg. Which of the following medications could have most likely prevented the neurological complications this patient developed in the hospital?

- A. ACE inhibitor (8%)
- B. Beta-adrenergic blocker (6%)
- ✓ C. Calcium channel blocker (55%)
- D. Central sympatholytic (4%)
- E. Nitrate (4%)
- F. Osmotic diuretic (18%)
- G. Thiazide diuretic (2%)

Omitted
Correct answer
C

55%
Answered correctly

01 sec
Time Spent

04/07/2020
Last Updated

Explanation

This patient with **subarachnoid hemorrhage** (SAH) developed new-onset focal neurological deficits 5 days after his initial symptoms; a presentation characteristic of delayed cerebral ischemia due to cerebral vasospasm. SAH is most often caused by the rupture of a **saccular**

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This patient with **subarachnoid hemorrhage** (SAH) developed new-onset focal neurological deficits 5 days after his initial symptoms; a presentation characteristic of delayed cerebral ischemia due to cerebral vasospasm. SAH is most often caused by the rupture of a **saccular (berry) aneurysm**, which occurs frequently in patients with autosomal dominant polycystic disease.

Cerebral vasospasm with subsequent ischemia is the most common complication of SAH and typically manifests **3-12 days** after the initial incident with a change in mental status and/or new **focal neurological deficits**. Nimodipine, a selective **calcium channel blocker**, improves outcomes in patients with SAH by preventing or reducing the extent of ischemic neurological deficits caused by cerebral vasospasm. This **neuroprotective** effect is likely due to a combination of increased cerebral vasodilation and decreased calcium-dependent excitotoxicity.

(Choices A and B) Enalapril (an ACE inhibitor) and labetalol (a beta-adrenergic blocker with some alpha-antagonist activity) can be used to control hypertension (lowering the chance of rebleeding) in patients after SAH. However, rebleeding usually occurs in the first 24 hours after SAH, and acute onset of new neurological deficits 5 days after SAH is more indicative of delayed ischemia due to cerebral vasospasm.

(Choice D) Central sympatholytics (eg, methyldopa, clonidine) stimulate alpha-2A receptors centrally, resulting in a decrease in generalized sympathetic outflow and reduced blood pressure. They do not have a role in prevention of ischemic deficits due to cerebral vasospasm following SAH.

(Choice E) Nitrates (eg, nitroglycerin, isosorbide mononitrate) are used as vasodilators primarily for the treatment of angina pectoris. In patients with a recent SAH, nitrates should be avoided because they can increase cerebral blood flow and intracranial pressure, which can worsen bleeding.

(Choice F) Osmotic diuretics (eg, mannitol) are part of the treatment for increased intracranial pressure (ICP). Although hydrocephalus can be a complication of SAH and result in elevated ICP, it typically presents with a gradual change in level of consciousness accompanied by ocular changes (eg, downward eye deviation, miosis) rather than focal extremity deficits. Ventricular dilation on neuroimaging is diagnostic.

(Choice G) Thiazide diuretics are a first-line therapy for essential hypertension in the outpatient setting. They are not indicated for use in preventing complications due to cerebral vasospasm following SAH.

Educational objective:
Delayed cerebral ischemia due to cerebral vasospasm usually presents 3-12 days after the initial subarachnoid hemorrhage (SAH) with an acute change in mental status and/or new focal neurological deficits. Nimodipine, a selective calcium channel blocker, improves outcomes in patients

and acute onset of new neurological deficits 5 days after SAH is more indicative of delayed ischemia due to cerebral vasospasm.

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Educational objective:
Delayed cerebral ischemia due to cerebral vasospasm usually presents 3-12 days after the initial subarachnoid hemorrhage (SAH) with an acute change in mental status and/or new focal neurological deficits. Nimodipine, a selective calcium channel blocker, improves outcomes in patients with cerebral vasospasm by inducing cerebral vasodilation and decreasing calcium-dependent excitotoxicity.

References

- Nimodipine and its use in cerebrovascular disease: evidence from recent preclinical and controlled clinical studies.
- Calcium antagonists for aneurysmal subarachnoid haemorrhage.

Pharmacology	Nervous System	Subarachnoid hemorrhage
Subject	System	Topic

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A new inhaled agent (drug A) is tested in an experiment designed to characterize its properties as a general anesthetic. Drug A's partial pressure in arterial blood is shown on the graph below as a function of time after beginning inhalation. A similar curve for nitrous oxide is also shown. Both drugs are administered at the same partial pressure in the inspired gas.

Which of the following best describes the properties of the new anesthetic as compared to nitrous oxide?

A. Fast equilibration with the brain

B. High blood/gas partitioning coefficient

C. Low potency

D. Low solubility in the blood

E. Rapid onset of action

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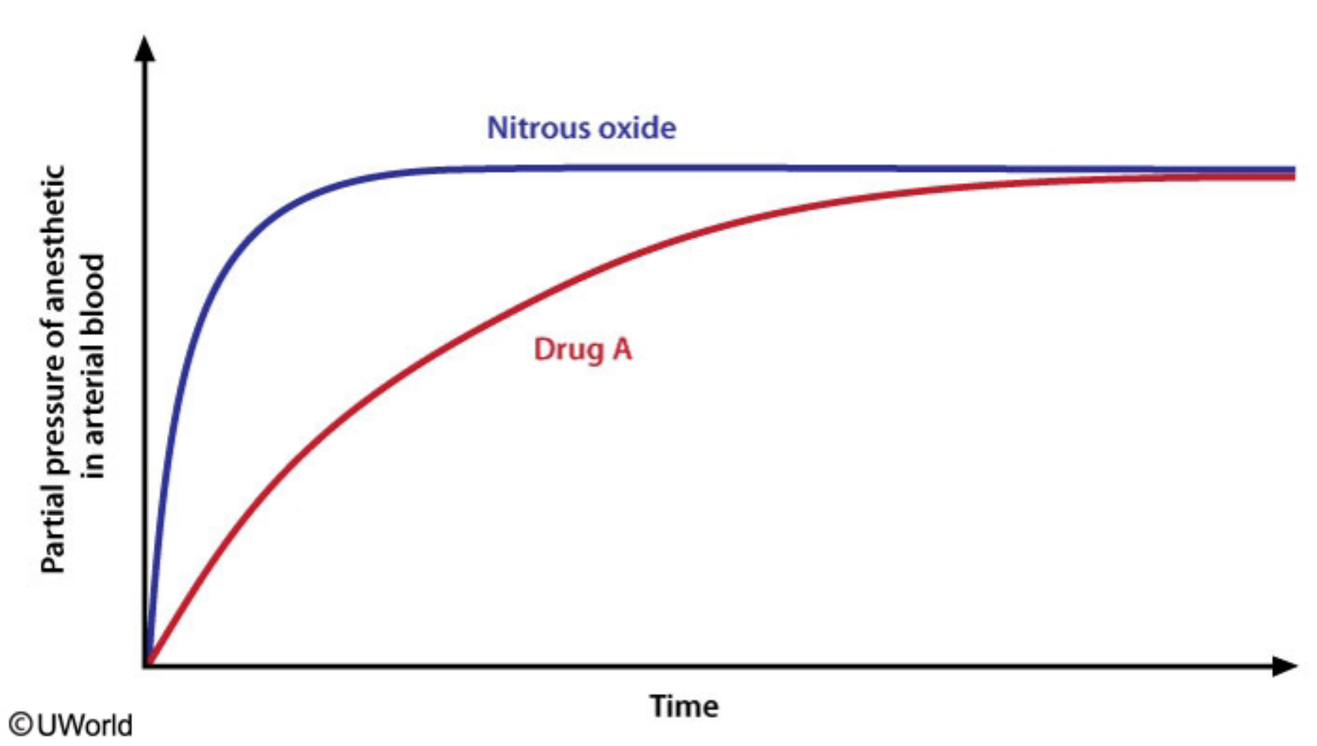
A new inhaled agent (drug A) is tested in an experiment designed to characterize its properties as a general anesthetic. Drug A's partial pressure in arterial blood is shown on the graph below as a function of time after beginning inhalation. A similar curve for nitrous oxide is also shown. Both drugs are administered at the same partial pressure in the inspired gas.



Which of the following best describes the properties of the new anesthetic as compared to nitrous oxide?

A. Fast equilibration with the brain

B. High blood/gas partitioning coefficient

C. Low potency

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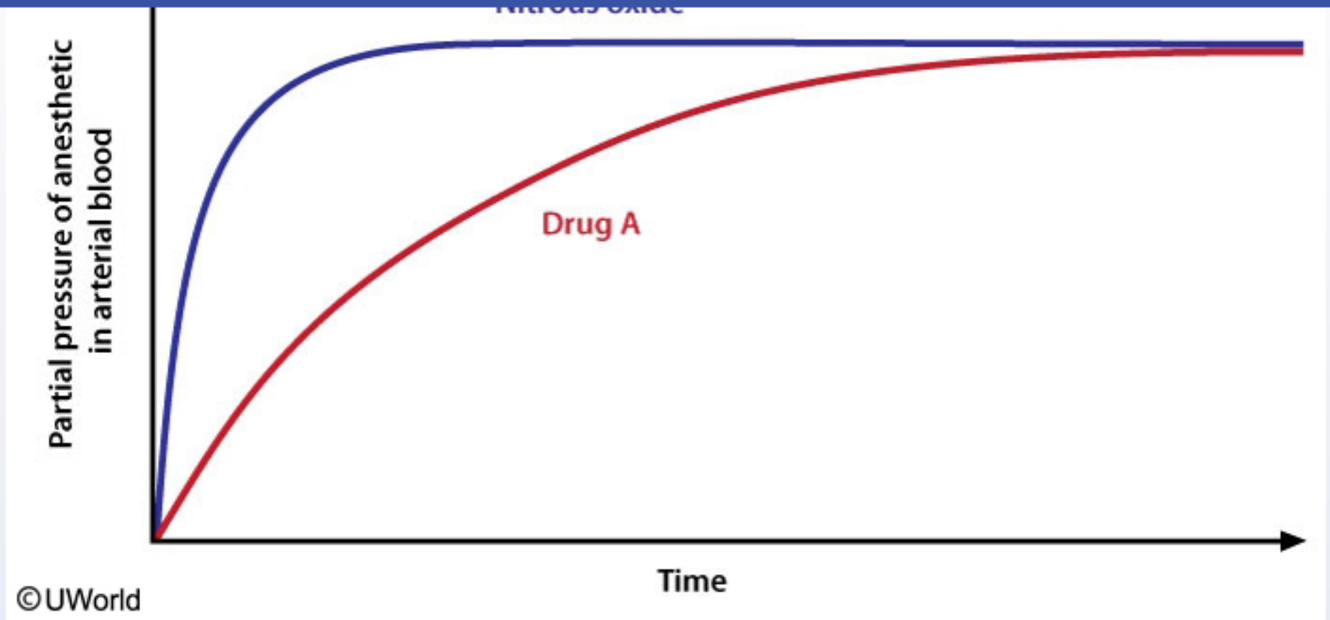

Which of the following best describes the properties of the new anesthetic as compared to nitrous oxide?

- A. Fast equilibration with the brain
- B. High blood/gas partitioning coefficient
- C. Low potency
- D. Low solubility in the blood
- E. Rapid onset of action

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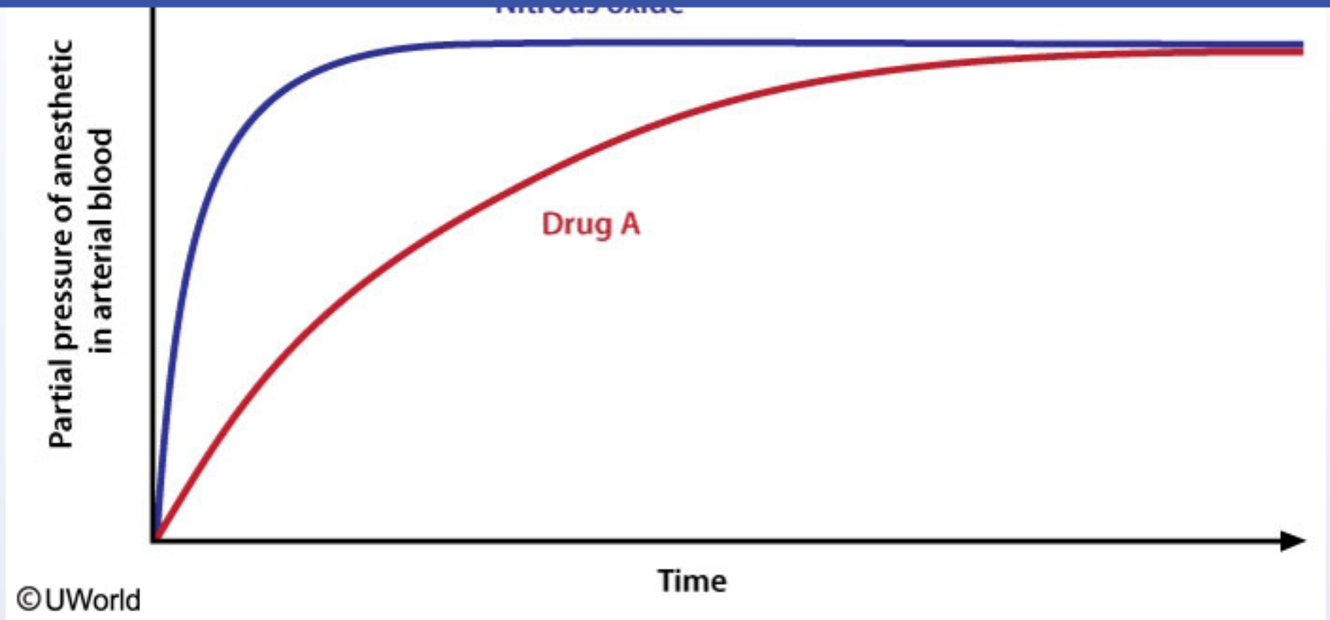

Which of the following best describes the properties of the new anesthetic as compared to nitrous oxide?

- A. Fast equilibration with the brain (4%)
- ✓ B. High blood/gas partitioning coefficient (37%)
- C. Low potency (17%)
- D. Low solubility in the blood (33%)
- E. Rapid onset of action (7%)

Omitted
Correct answer

37%
Answered correctly

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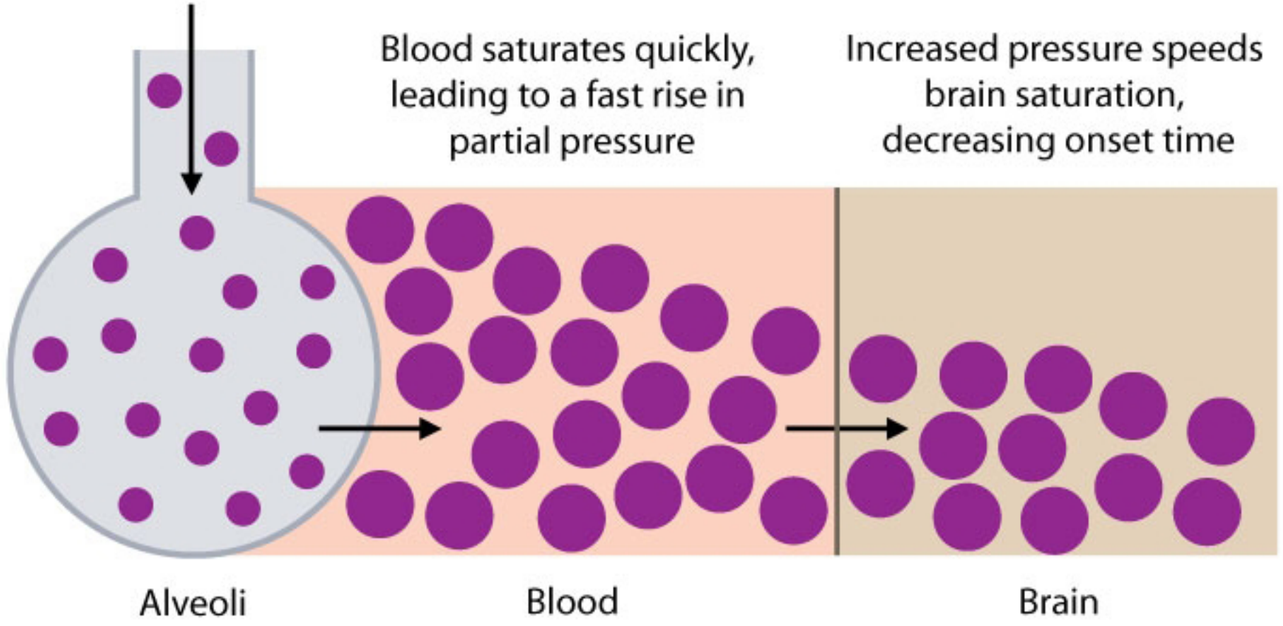
Effects of solubility on the onset of gas anesthetics

Poorly soluble gas (↓blood/ gas partition coefficient)



Highly soluble gas (↑blood/ gas partition coefficient)

Blood saturates slowly, leading to a delayed rise in

Decreased pressure slows brain saturation,

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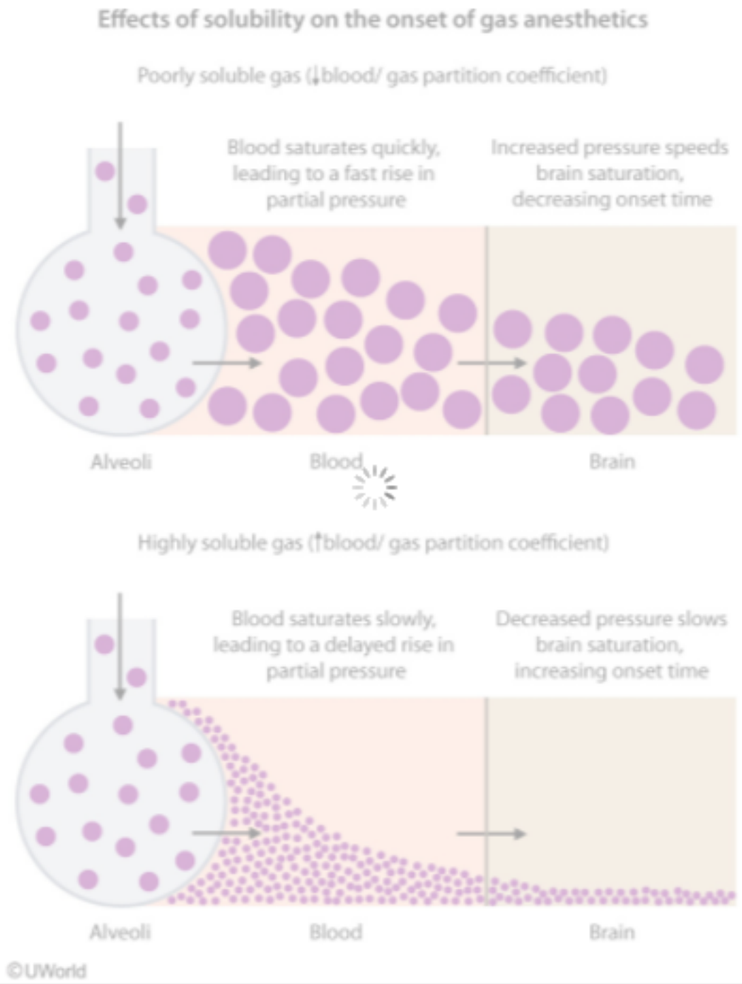

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leading to a delayed rise in brain saturation.

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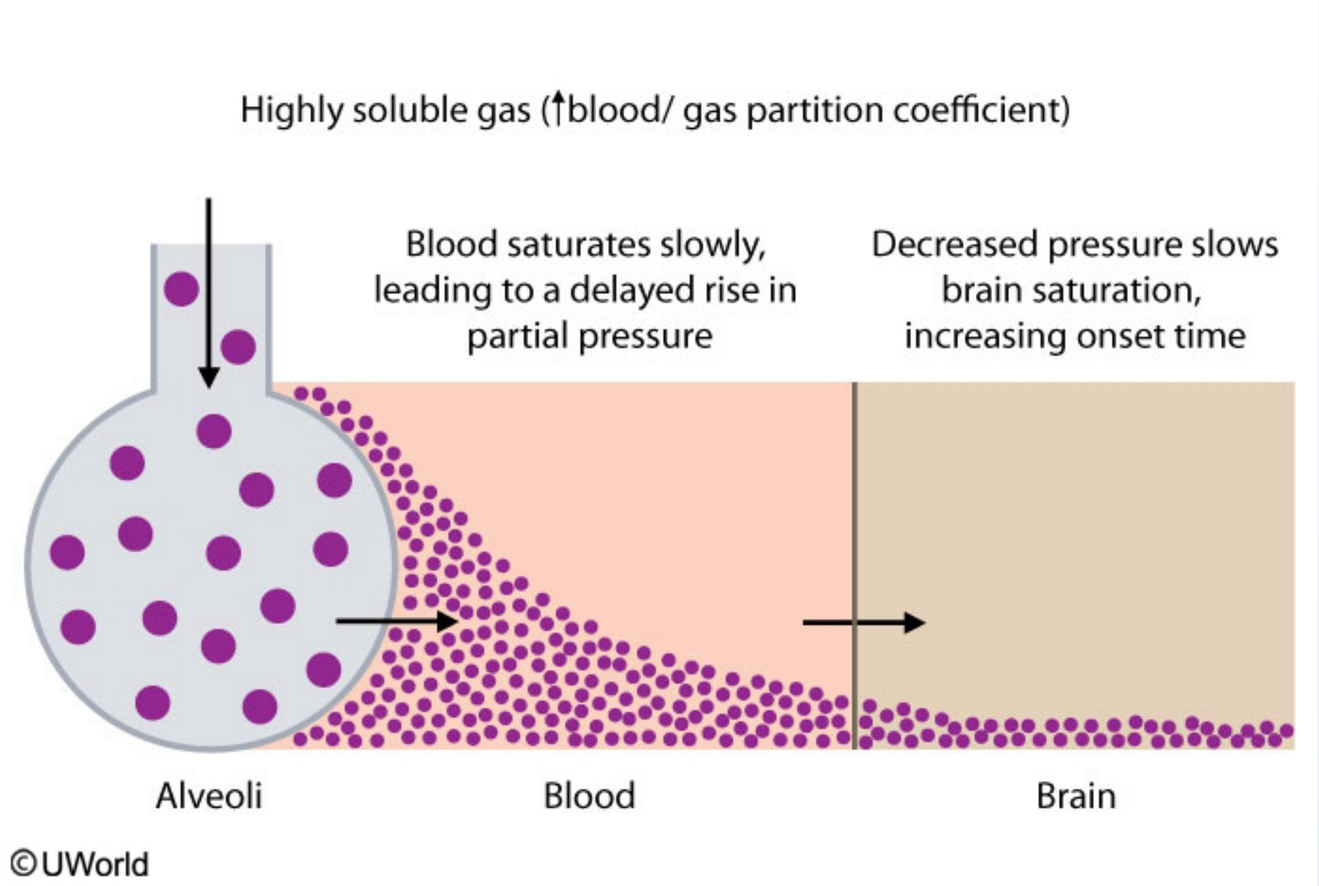

During anesthetic induction with a gaseous agent, the partial pressure of the anesthetic rises in the blood until it reaches its partial pressure in the inspired gas. At this point, no more of the anesthetic can dissolve in the blood and the blood is said to be saturated with the anesthetic. The speed at which the blood becomes saturated depends on the solubility of the gas in the blood. Highly soluble anesthetics dissolve easily in the blood, and thus larger amounts must be absorbed before the blood becomes saturated.

Blood solubility of an anesthetic is indicated by its **blood/gas partition coefficient** - anesthetics with higher blood solubility have larger blood/gas partition coefficients. Nitrous oxide (N_2O) is an example of a poorly soluble gas with a blood/gas partition coefficient of 0.47. In the graph above, the partial pressure of N_2O in blood rises rapidly and plateaus, indicating that the blood quickly becomes saturated with the anesthetic. In

During anesthetic induction with a gaseous agent, the partial pressure of the anesthetic rises in the blood until it reaches its partial pressure in the inspired gas. At this point, no more of the anesthetic can dissolve in the blood and the blood is said to be saturated with the anesthetic. The speed at which the blood becomes saturated depends on the solubility of the gas in the blood. Highly soluble anesthetics dissolve easily in the blood, and thus larger amounts must be absorbed before the blood becomes saturated.

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The speed of anesthetic induction is determined by the rate at which the brain tissues take up the agent, which is dependent on the solubility of the anesthetic in the blood. If an agent has poor blood solubility, the amount of gas needed to saturate the blood is small and brain saturation occurs fairly quickly. Conversely, highly soluble anesthetics are absorbed to a greater degree by the blood, delaying saturation of the central nervous system.

Characteristics of gas anesthetics

Effect	Poorly soluble gas (N_2O)	Highly soluble gas (halothane)
Amount needed to saturate the blood	Small	Large
Rise in partial pressure in blood	Rapid	Slow
Equilibration with the brain	Rapid	Slow

nervous system.

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Rise in partial pressure in blood	Rapid	Slow
Equilibration with the brain	Rapid	Slow
Onset of action	Rapid	Slow

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(Choices A, D, and E) Nitrous oxide is an example of a gas with relatively low solubility in the blood. It is characterized by rapid onset of action and fast equilibration with the brain.

(Choice C) Potency of a gas anesthetic is determined by the minimal alveolar concentration. It is defined as the concentration of gas in the lungs that produces the desired effect in 50% of patients. Potent anesthetics require lower partial pressures to be effective.

Educational objective:
The onset of action of a gas anesthetic depends on its solubility in the blood (blood/gas partition coefficient). Drugs with high blood/gas partition coefficients are more soluble in the blood, demonstrate slower equilibration with the brain, and have longer onset times.

Pharmacology Nervous System Drug structure and properties

Effect	Poorly soluble gas (N_2O)	Highly soluble gas (halothane)
Amount needed to saturate the blood	Small	Large
Rise in partial pressure in blood	Rapid	Slow
Equilibration with the brain	Rapid	Slow
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Educational objective:
The onset of action of a gas anesthetic depends on its solubility in the blood (blood/gas partition coefficient). Drugs with high blood/gas partition coefficients are more soluble in the blood, demonstrate slower equilibration with the brain, and have longer onset times.

Pharmacology	Nervous System	Drug structure and properties
Subject	System	Topic

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A 43-year-old male with multiple medical problems including seizure disorder and mental illness comes to your office for the first time in order to establish a primary care physician. On routine physical examination, you notice the findings shown in the photo below.

Which of the following is most likely responsible for the condition of this patient's teeth and gums?

A. Phenytoin
B. Lithium
C. Prednisone
D. Cocaine
E. Methimazole
F. Clozapine

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Which of the following is most likely responsible for the condition of this patient's teeth and gums?

- A. Phenytoin (82%)
- B. Lithium (5%)
- C. Prednisone (1%)
- D. Cocaine (4%)
- E. Methimazole (2%)
- F. Clozapine (3%)

Omitted
Correct answer

82%
Answered correctly

10 secs
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Gingival hyperplasia, like that shown in the photo above, is a common side effect of phenytoin. It occurs in 50% of patients who have had 3-4 months of phenytoin therapy. The mechanism of this side effect is associated with increased expression of platelet-derived growth factor (PDGF). When gingival macrophages are exposed to increased amounts of PDGF, they stimulate proliferation of gingival cells and alveolar bone. Gingival hyperplasia may regress after discontinuation of phenytoin.

Phenytoin is an anticonvulsant effective in the treatment of grand mal (tonic-clonic) seizures, partial seizures, and status epilepticus. Phenytoin inhibits abnormal electrical activity of the brain by blocking voltage-gated sodium channels in neurons. Phenytoin has a narrow therapeutic index with a number of potential adverse effects:

1. Phenytoin toxicity is mainly characterized by CNS manifestations. Its effect on the cerebellum and vestibular system can cause ataxia and nystagmus.
2. Long-term therapy with phenytoin may cause gingival hyperplasia, coarsening of the facial features, and hirsutism.
3. Phenytoin interferes with the metabolism of folic acid and may cause megaloblastic anemia.
4. Phenytoin induces the P450 cytochrome oxidase system. It increases the metabolism—and therefore decreases the blood level—of many medications.
5. If taken during pregnancy, phenytoin may cause fetal hydantoin syndrome.

(Choice B) Lithium also has a narrow therapeutic index. Lithium toxicity is associated with neuromuscular excitability (irregular coarse tremors, fascicular twitching, rigid motor agitation, and ataxia). It may also cause nephrogenic diabetes insipidus, hypothyroidism, and cardiac conduction defects, but not gingival hyperplasia.

(Choice C) The adverse effects of prednisone include hyperglycemia, weight gain, depression, fluid retention with edema, and osteoporosis.

(Choice D) Cocaine blocks the re-uptake of norepinephrine, serotonin, and dopamine in the CNS. It can cause cardiac ischemia, hypertension, and seizures. Cocaine withdrawal is associated with severe depression.

(Choice E) Methimazole inhibits thyroid hormone synthesis by suppressing the iodination and coupling of tyrosine. Side effects include edema, rash, and agranulocytosis.

(Choice F) Clozapine is an atypical antipsychotic that is most helpful in treating the negative symptoms of schizophrenia. The most serious side effects of clozapine include agranulocytosis and seizures.

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Educational Objective:
Gingival hyperplasia is a common side effect of phenytoin and is sometimes reversible when phenytoin is withdrawn. Phenytoin causes increased expression of platelet-derived growth factor (PDGF). When gingival macrophages are exposed to increased amounts of PDGF, they stimulate proliferation of gingival cells and alveolar bone. Phenytoin toxicity mainly affects the cerebellum and vestibular system, causing ataxia and nystagmus.

Pharmacology	Nervous System	Antiepileptics
Subject	System	Topic

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A 62-year-old woman is brought to the emergency department because of acute chest pain. She also complains of diaphoresis, nausea, and lightheadedness. Her blood pressure is 90/60 mm Hg and pulse is 42/min. An ECG reveals ST-segment elevation in the inferior leads. The appropriate therapy is initiated, including a medication to treat her bradycardia. After initial treatment, her blood pressure is 120/70 mm Hg and pulse is 76/min. However, she now complains of severe right-sided eye pain. Which of the following is the most likely cause for this patient's eye pain?

A. Iridocyclitis
B. Retinal artery thrombosis
C. Acute conjunctivitis
D. Glaucoma
E. Cataract
F. Retinal vein thrombosis
G. Retinal detachment
H. Vitreous hemorrhage

Submit

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- A. Iridocyclitis (2%)
- B. Retinal artery thrombosis (18%)
- C. Acute conjunctivitis (0%)
- ✓ D. Glaucoma (60%)
- E. Cataract (0%)
- F. Retinal vein thrombosis (6%)
- G. Retinal detachment (4%)
- H. Vitreous hemorrhage (6%)

Omitted
Correct answer
D

60%
Answered correctly

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Explanation

ST-segment elevation in the inferior leads is diagnostic of an inferior myocardial infarction (MI). Inferior MIs are often due to blockage of the right

ST-segment elevation in the inferior leads is diagnostic of an inferior myocardial infarction (MI). Inferior MIs are often due to blockage of the right coronary artery, the artery usually responsible for sinoatrial (SA) and atrioventricular (AV) node perfusion. Thus, inferior MIs are often associated with bradycardia. Atropine blocks vagal influence on the SA and AV nodes and is effective in increasing heart rate in such patients. Atropine's side effects are due to muscarinic receptor blockade in other organs. In the eye, atropine causes mydriasis, resulting in narrowing of the anterior chamber angle and diminished outflow of aqueous humor. This can precipitate angle-closure glaucoma in patients with shallow anterior chambers or higher than normal intraocular pressures. Acute closed-angle glaucoma presents with unilateral severe eye pain and visual disturbances (eg, halos). Individuals of Inuit and Asian descent are at increased risk of angle-closure glaucoma.

The clinical indications for anticholinergic medications are summarized in the table.

System	Effect	Clinical use
CNS	Sedation In toxic doses: psychosis	Motion sickness (scopolamine) Parkinson's disease (benztropine)
Eye	Mydriasis (dilated pupil) Cycloplegia (paralysis of accommodation)	Ophthalmologic examination Treatment of uveitis **Contraindicated in glaucoma!**
Heart	Tachycardia	Sinus bradycardia Heart block (atropine)
Secretions	↓ lacrimation, sweating, salivation, GI and bronchial secretions	Premedication before anesthesia (atropine, scopolamine)
Bladder	Detrusor relaxation, delays voiding	Neurogenic (spastic) bladder (oxybutynin)
Bronchi	Bronchodilatation	Asthma and COPD (ipratropium)

(Choice A) Anticholinergic medications (cycloplegics) reduce pain and prevent the formation of adhesions in iridocyclitis (uveitis). Atropine does not precipitate iridocyclitis.

(Choices B, E, F, G, and H) These conditions present with either loss of vision or visual disturbances. They are usually not painful and would not be affected by anticholinergic drugs.

Educational objective:
Atropine is indicated for the treatment of bradycardia as it decreases vagal influence on the SA and AV nodes. A common side effect is increased

halos). Individuals of Inuit and Asian descent are at increased risk of angle-closure glaucoma.

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(Choices B, E, F, G, and H) These conditions present with either loss of vision or visual disturbances. They are usually not painful and would not be affected by anticholinergic drugs.

Educational objective:
Atropine is indicated for the treatment of bradycardia as it decreases vagal influence on the SA and AV nodes. A common side effect is increased intraocular pressure. It may precipitate acute closed-angle glaucoma in susceptible individuals.

Pharmacology	Nervous System	Glaucoma
Subject	System	Topic

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A 72-year-old man with a history of Parkinson disease comes to the office for follow-up. The patient has been taking levodopa/carbidopa since being diagnosed 5 years ago, and has required increasing doses of medication to control his symptoms. He is currently on a maximum dose, but for the past several months has experienced bothersome motor fluctuations. The patient also reports worsening stiffness and difficulty moving before his next scheduled dose, which improves after taking the medication. Entacapone is added to his treatment regimen. This drug most likely improves this patient's symptoms by which of the following mechanisms?

A. Decreasing peripheral levodopa degradation

B. Directly stimulating dopamine receptors

C. Enhancing the effect of endogenous dopamine

D. Inhibiting central muscarinic receptors

E. Inhibiting centrally-active acetylcholinesterase

Submit

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- ✓ A. Decreasing peripheral levodopa degradation (61%)
- B. Directly stimulating dopamine receptors (9%)
- C. Enhancing the effect of endogenous dopamine (18%)
- D. Inhibiting central muscarinic receptors (5%)
- E. Inhibiting centrally-active acetylcholinesterase (5%)

Omitted
Correct answer
A

61%
Answered correctly

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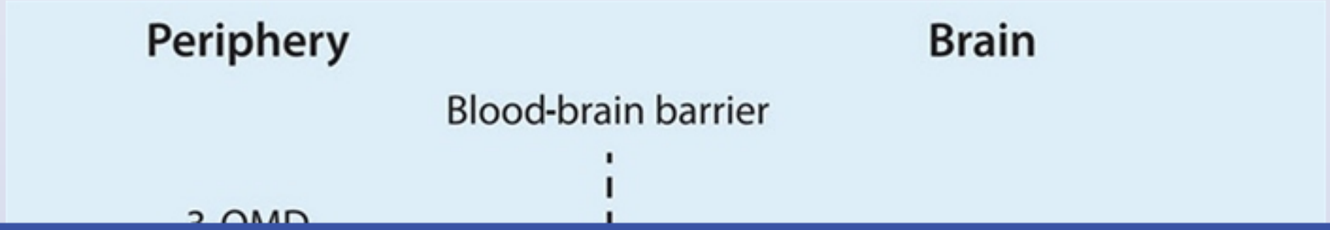
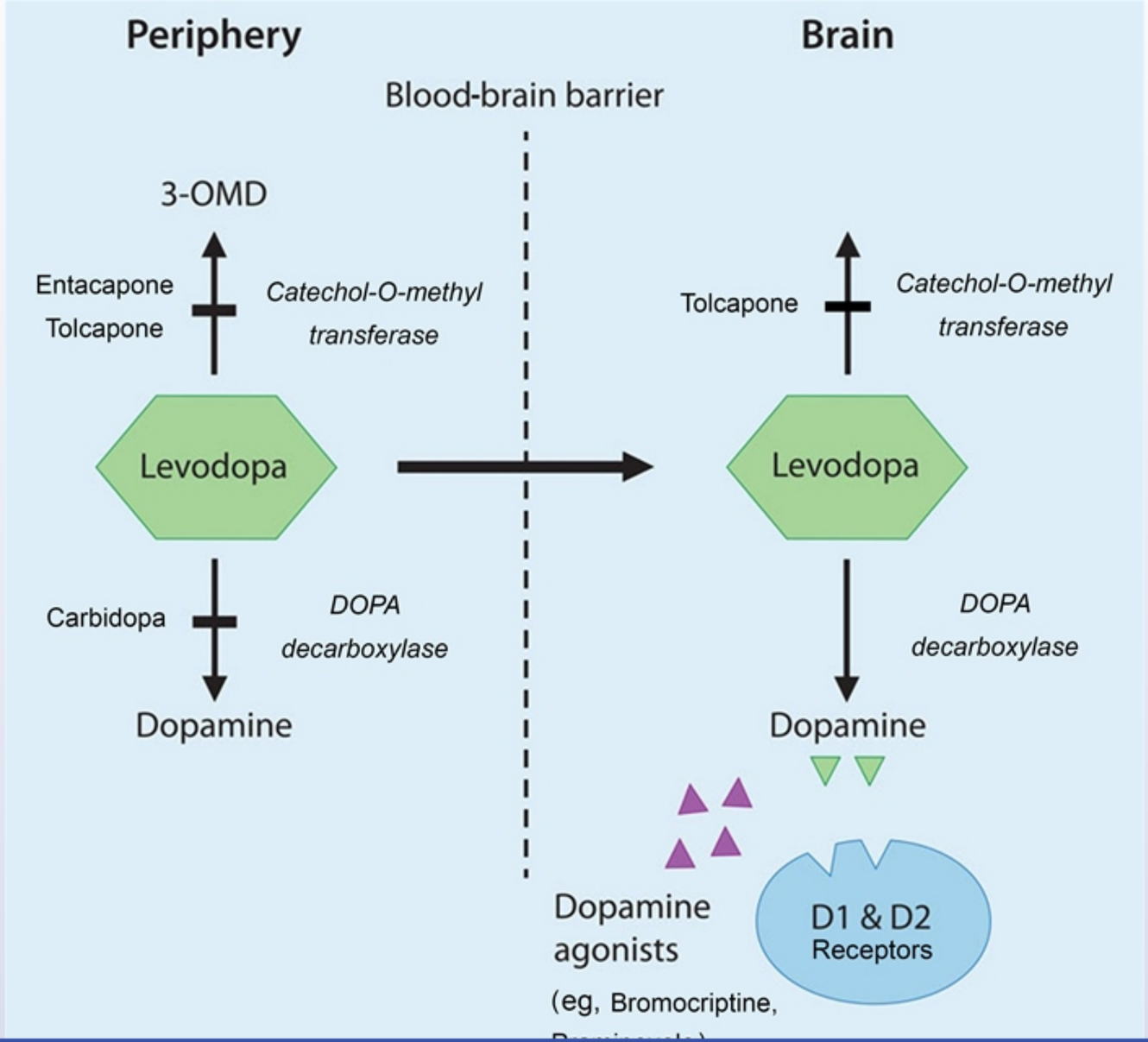
Explanation




Periphery
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Blood-brain barrier
3-OMD
Entacapone
Tolcapone
Catechol-O-methyl transferase
Levodopa
Carbidopa
DOPA decarboxylase
Dopamine
Tolcapone
Catechol-O-methyl transferase
Levodopa
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Dopamine agonists
(eg, Bromocriptine,
D1 & D2 Receptors

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Levodopa is the immediate precursor of dopamine, a neurotransmitter that is absent in the nigrostriatum of patients with **Parkinson disease**. Dopamine itself cannot be administered directly due to its inability to cross the blood-brain barrier; however, levodopa can cross this barrier. Levodopa is rapidly metabolized in the peripheral tissues to dopamine (via DOPA decarboxylase) and 3-O-methyldopa (via catechol-O-methyltransferase [COMT]). Therefore, only a small percentage of levodopa reaches the brain. Consequently, levodopa is typically administered with carbidopa, a peripheral DOPA decarboxylase inhibitor, but even then only 5%-10% of levodopa reaches the brain.

Entacapone is a **COMT inhibitor** that increases the bioavailability of levodopa by inhibiting its **peripheral** methylation. Combining levodopa with entacapone helps increase the plasma half-life of levodopa, producing more stable levodopa plasma concentrations and prolonging the therapeutic effect of each dose. COMT inhibitors are currently used to treat Parkinson disease patients with motor fluctuations who are experiencing end-of-dose "wearing off" periods with levodopa/carbidopa therapy. COMT inhibitors should only be used in combination with levodopa, as they are otherwise ineffective.

(Choice B) Dopamine agonists (eg, bromocriptine, pramipexole, ropinirole) preferentially stimulate dopamine 2 receptors.

(Choice C) Amantadine likely enhances the effect of endogenous dopamine by increasing dopamine synthesis/release and inhibiting the reuptake of dopamine.

(Choice D) Anticholinergics such as trihexyphenidyl and benztropine inhibit central muscarinic receptors. These drugs are mainly used for drug-induced parkinsonism, but patients with tremor as the predominant symptom also respond well.

(Choice E) Acetylcholinesterase inhibitors (eg, donepezil, rivastigmine) increase the amount of acetylcholine in the central nervous system. These drugs are commonly used in patients with dementia to increase cholinergic activity in the prefrontal cortex. However, they should be used cautiously in patients with Parkinson disease as higher levels of acetylcholine in the basal ganglia can exacerbate symptoms.

Educational objective:
Parkinson disease is typically treated with levodopa (immediate precursor of dopamine), which crosses the blood-brain barrier. Levodopa is administered with DOPA decarboxylase inhibitors (eg, carbidopa) and sometimes catechol-O-methyltransferase inhibitors (eg, entacapone) to reduce the peripheral metabolism of levodopa, resulting in increased levodopa bioavailability to the brain.

References

- Pharmacological treatment of Parkinson disease: A review.

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Entacapone is a **COMT inhibitor** that increases the bioavailability of levodopa by inhibiting its **peripheral** methylation. Combining levodopa with entacapone helps increase the plasma half-life of levodopa, producing more stable levodopa plasma concentrations and prolonging the therapeutic effect of each dose. COMT inhibitors are currently used to treat Parkinson disease patients with motor fluctuations who are experiencing end-of-dose "wearing off" periods with levodopa/carbidopa therapy. COMT inhibitors should only be used in combination with levodopa, as they are otherwise ineffective.

(Choice B) Dopamine agonists (eg, bromocriptine, pramipexole, ropinirole) preferentially stimulate dopamine 2 receptors.

(Choice C) Amantadine likely enhances the effect of endogenous dopamine by increasing dopamine synthesis/release and inhibiting the reuptake of dopamine.

(Choice D) Anticholinergics such as trihexyphenidyl and benztropine inhibit central muscarinic receptors. These drugs are mainly used for drug-induced parkinsonism, but patients with tremor as the predominant symptom also respond well.

(Choice E) Acetylcholinesterase inhibitors (eg, donepezil, rivastigmine) increase the amount of acetylcholine in the central nervous system. These drugs are commonly used in patients with dementia to increase cholinergic activity in the prefrontal cortex. However, they should be used cautiously in patients with Parkinson disease as higher levels of acetylcholine in the basal ganglia can exacerbate symptoms.

Educational objective:
Parkinson disease is typically treated with levodopa (immediate precursor of dopamine), which crosses the blood-brain barrier. Levodopa is administered with DOPA decarboxylase inhibitors (eg, carbidopa) and sometimes catechol-O-methyltransferase inhibitors (eg, entacapone) to reduce the peripheral metabolism of levodopa, resulting in increased levodopa bioavailability to the brain.

References

- Pharmacological treatment of Parkinson disease: A review.

Pharmacology	Nervous System	Parkinson disease
Subject	System	Topic

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A 78-year-old man was found to have a perihilar mass on screening CT scan. The patient's medical history is remarkable for chronic obstructive pulmonary disease, for which he takes albuterol inhalers as needed. He has smoked a pack of cigarettes daily for the last 50 years and does not drink alcohol or use illicit drugs. The patient is admitted for bronchoscopy and is premedicated with intramuscular atropine and becomes acutely restless, disoriented, and combative. Temperature is 38.1 C (100.5 F), blood pressure is 116/72 mm Hg, pulse is 110/min, and respirations are 15/min. Oxygen saturation is 99% on room air. On physical examination, his pupils are widely dilated and nonreactive to light. ECG shows sinus tachycardia. Which of the following agents will reverse all of this patient's signs and symptoms?

A. Diazepam
B. Edrophonium
C. Haloperidol
D. Neostigmine
E. Physostigmine

Submit

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A. Diazepam (4%)
B. Edrophonium (8%)
C. Haloperidol (2%)
D. Neostigmine (13%)
✓ E. Physostigmine (72%)

Omitted
Correct answer
E

72%
Answered correctly

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Time Spent

02/01/2020
Last Updated

Explanation

Anticholinergic toxicity	
Symptom	Mechanism
"Hot as a hare"	

Anticholinergic toxicity

Symptom	Mechanism
"Hot as a hare" ↑ Body temperature	↓ Sweating leads to ↓ heat dissipation
"Dry as a bone" ↓ Secretions (eg, mucous membranes, sweat glands)	↓ Glandular secretion & smooth muscle contraction
"Red as a beet" Flushed skin	Superficial vasodilation from ↑ body heat
"Blind as a bat" Cycloplegia, mydriasis	Paralysis of ciliary muscle & iris sphincter
"Mad as a hatter" Altered mental status	Permeates blood-brain barrier & affects CNS pathways
"Full as a flask" Urinary retention Constipation	↓ Detrusor contraction & ↓ internal urethral sphincter relaxation ↓ Intestinal smooth muscle contraction
"Fast as a fiddle" Tachycardia	↓ Vagal tone at the sinoatrial node

Atropine is an anticholinergic medication that can be administered prior to bronchoscopy to decrease respiratory mucus secretions and promote bronchodilation. **Anticholinergic** drugs competitively inhibit the muscarinic acetylcholine receptor both centrally (leading to delirium, coma, and respiratory failure) and peripherally (see toxidrome in table). The elderly are at particularly high risk of developing anticholinergic toxicity, likely due to decreased renal and hepatic clearance.

Cholinesterase inhibitors overcome this toxicity by inhibiting the degradation of acetylcholine, thereby increasing the concentration of acetylcholine at the synaptic cleft. Central nervous system (CNS) penetration and reversal of central symptoms are dependent on chemical

Tachycardia	↓ Vagal tone at the sinoatrial node

Atropine is an anticholinergic medication that can be administered prior to bronchoscopy to decrease respiratory mucus secretions and promote bronchodilation. **Anticholinergic** drugs competitively inhibit the muscarinic acetylcholine receptor both centrally (leading to delirium, coma, and respiratory failure) and peripherally (see toxidrome in table). The elderly are at particularly high risk of developing anticholinergic toxicity, likely due to decreased renal and hepatic clearance.

Cholinesterase inhibitors overcome this toxicity by inhibiting the degradation of acetylcholine, thereby increasing the concentration of acetylcholine at the synaptic cleft. Central nervous system (CNS) penetration and reversal of central symptoms are dependent on chemical structure:

- **Tertiary amines** (eg, **physostigmine**, galantamine, donepezil, rivastigmine) are lipophilic (nonpolar) and can easily cross the blood-brain barrier to reverse both central and peripheral symptoms.
- Quaternary amines (eg, neostigmine, edrophonium, pyridostigmine) are hydrophilic (polarized) and do not readily cross the blood-brain barrier. These drugs reverse peripheral symptoms only **(Choices B and D)**.

(Choices A and C) Both diazepam and haloperidol can be used for sedation or cases of severe agitation. Haloperidol is an antipsychotic that blocks dopamine receptors in the CNS, and diazepam is a long-acting benzodiazepine that positively modulates GABA-A activity. Neither medication reverses the peripheral anticholinergic manifestations (eg, mydriasis, tachycardia).

Educational objective:
Physostigmine is a cholinesterase inhibitor with a tertiary ammonium structure that can reverse both the central and peripheral nervous system symptoms of anticholinergic toxicity. Neostigmine, edrophonium, and pyridostigmine have a quaternary ammonium structure that limits central nervous system penetration.

Pharmacology	Nervous System	Anticholinergics
Subject	System	Topic

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A 24-year-old man comes to the emergency department after injuring his shoulder. He was standing on a ladder hanging pictures in his living room when he lost his balance and fell, impacting his left shoulder on the hardwood floor. Radiographs show an anterior dislocation of the humerus. Reduction of the patient's dislocated joint is performed under procedural sedation with intravenous propofol. A single bolus of propofol provides adequate sedation for the procedure, and he becomes clinically alert several minutes after administration. Which of the following mechanisms most likely explains this patient's rapid recovery from anesthesia?

A. Liver elimination of the drug

B. Lung elimination of the drug

C. Renal elimination of the drug

D. Spontaneous degradation in plasma

E. Tissue redistribution of the drug

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- A. Liver elimination of the drug (12%)
- B. Lung elimination of the drug (8%)
- C. Renal elimination of the drug (6%)
- D. Spontaneous degradation in plasma (9%)
- ✓ E. Tissue redistribution of the drug (64%)

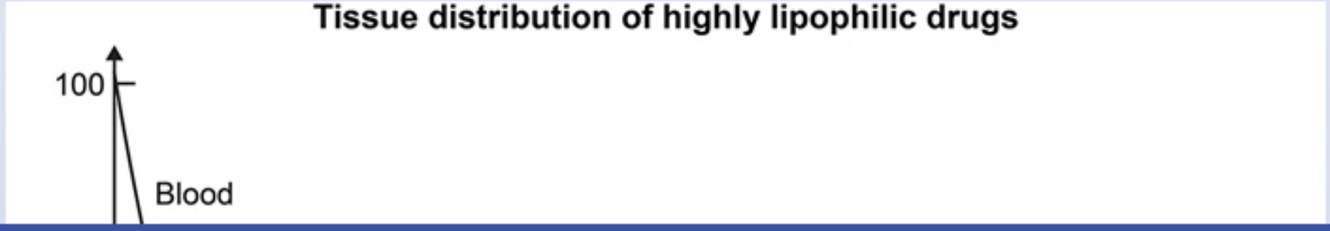
Omitted
Correct answer
E

64%
Answered correctly

02 secs
Time Spent

04/26/2020
Last Updated

Explanation



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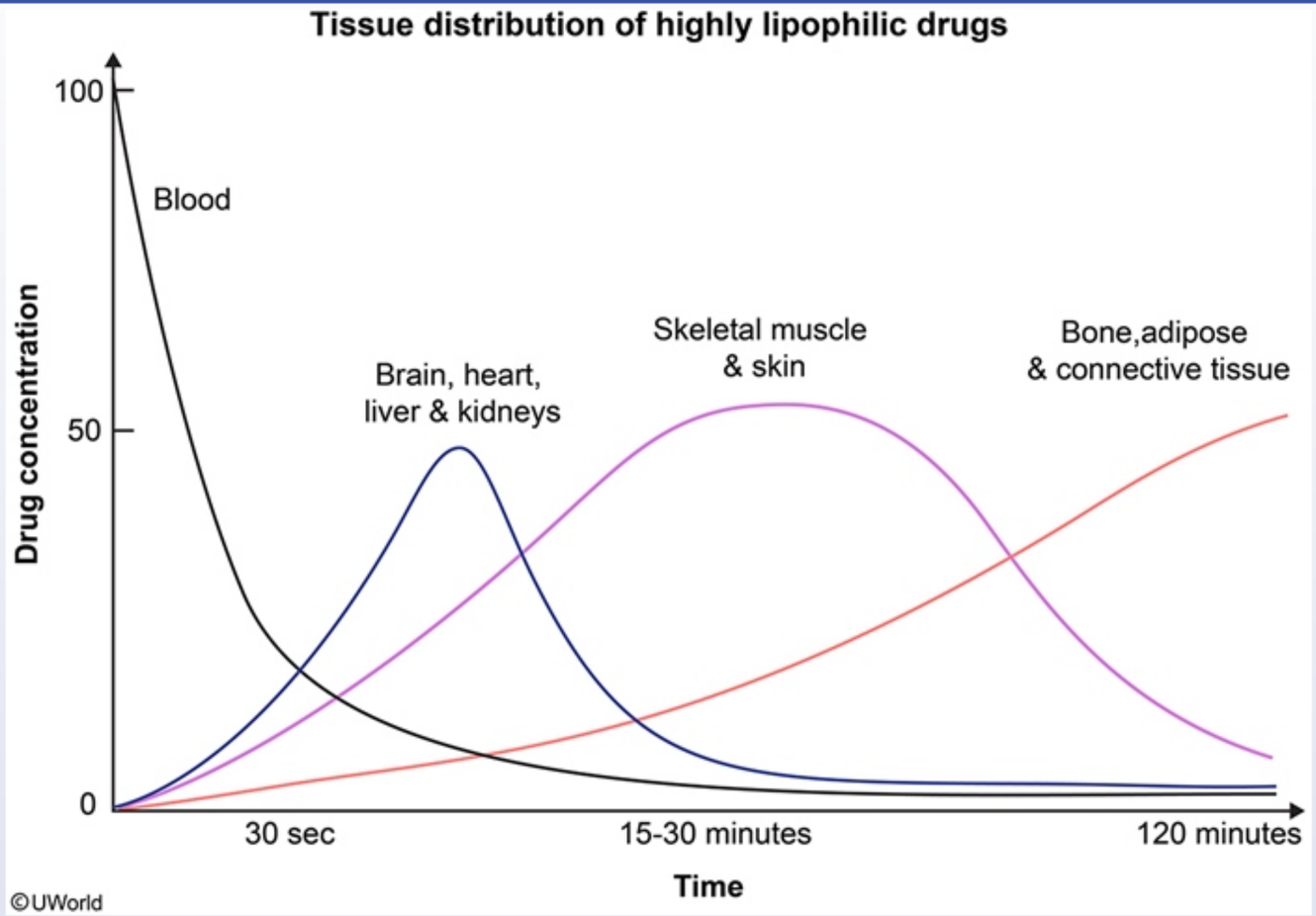

Propofol is a highly lipophilic anesthetic drug used for both induction and maintenance of general anesthesia as well as procedural sedation. When administered as an intravenous bolus, its onset of action is approximately 30 seconds with a duration of action typically lasting <10 minutes. Administration causes a rapid decrease in the level of consciousness as well as a global amnestic effect.

Following bolus infusion, propofol is rapidly cleared from the plasma and **preferentially distributed** to organs receiving **high blood flow** (eg, brain). This initial distribution accounts for the rapid onset of sedation seen with its administration. Over time, propofol is **redistributed** to organs receiving less blood flow (eg, fat, muscle tissue). Because the site of action for propofol is the brain, redistribution accounts for the rapid

Propofol is a highly lipophilic anesthetic drug used for both induction and maintenance of general anesthesia as well as procedural sedation. When administered as an intravenous bolus, its onset of action is approximately 30 seconds with a duration of action typically lasting <10 minutes. Administration causes a rapid decrease in the level of consciousness as well as a global amnestic effect.

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(Choice A) Although propofol is metabolized in the liver through hepatic conjugation, its half-life is 4 hours to 1 day; therefore, hepatic metabolism does not occur fast enough to account for such a short duration of action.

(Choice B) Volatile, inhaled anesthetics such as halothane are predominately eliminated by the lungs.

(Choice C) Renal tubular secretion and glomerular filtration are the predominate mechanisms through which water-soluble drugs are eliminated.

(Choice D) Atracurium is a non-depolarizing neuromuscular blocking agent that spontaneously degrades in plasma and organ tissue, a type of metabolism known as Hofmann elimination.

Educational objective

Propofol and other highly lipophilic drugs readily diffuse across membranes, quickly accumulating in tissues receiving high blood flow; this accounts for their rapid onset of action. These compounds are subsequently redistributed to organs receiving less blood flow, which explains their short duration of action.

References

- Propofol. A review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anesthetic

Pharmacology	Nervous System	Anesthesia
Subject	System	Topic

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A 23-year-old female is brought to the ER after having a tonic-clonic seizure. She has a history of seizures and takes phenytoin. She does not use tobacco, alcohol or illicit drugs. On physical examination, no focal abnormalities are noted. Blood tests reveal her plasma phenytoin level to be low. She states that she has been compliant with her medication. Which of the following drugs may be responsible for this patient's condition if co-administered with phenytoin?

A. Amoxicillin
B. Rifampin
C. Metronidazole
D. Fluconazole
E. Cimetidine
F. Omeprazole
G. Oral contraceptives

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A. Amoxicillin (0%)
✓ B. Rifampin (65%)
C. Metronidazole (1%)
D. Fluconazole (3%)
E. Cimetidine (13%)
F. Omeprazole (2%)
G. Oral contraceptives (12%)

Omitted
Correct answer
B

65%
Answered correctly

01 sec
Time Spent

01/14/2020
Last Updated

Explanation

As with many other medications, phenytoin is metabolized by hepatic P450 oxidase. Plasma drug level, efficacy, and the severity of side effects are directly influenced by the rate of metabolism of phenytoin. The following features of phenytoin metabolism are important:

As with many other medications, phenytoin is metabolized by hepatic P450 oxidase. Plasma drug level, efficacy, and the severity of side effects are directly influenced by the rate of metabolism of phenytoin. The following features of phenytoin metabolism are important:

1. Hepatic hydroxylation of phenytoin is **dose-dependent.** When low doses of phenytoin are administered, a sufficient number of enzyme molecules are available, and the drug is eliminated rapidly. Higher doses of phenytoin may fully saturate the enzyme; hence, increasing the dose above the saturation limit causes an inability to metabolize the drug and a rapid rise in plasma levels. Even a small increase in phenytoin intake above the prescribed dose may lead to severe toxicity.
2. Phenytoin is **an inducer of P450 oxidase**. Induction of this enzyme increases the consumption of many medications that are metabolized by the liver, such as oral contraceptives. When the P450 oxidase system is induced, the serum concentration of such medications will decrease, thereby reducing efficacy.
3. Because phenytoin is metabolized by P450 enzymes, its level is affected when it is co-administered with other medications that induce or inhibit the P450 system. The co-administration of phenytoin with P450 inducers decreases concentration of phenytoin in plasma and diminishes its effectiveness. Some **P450 inducers** are barbiturates, rifampin, carbamazepine, griseofulvin, and chronic alcohol consumption. P450 inhibitors slow hepatic metabolism, which increases the toxicity of phenytoin. Some of **P450 inhibitors** are isoniazid, cimetidine, macrolides, azole antifungals, and grapefruit juice.

(Choices A) Amoxicillin do not affect the hepatic metabolism of phenytoin.

(Choices C and G) Both metronidazole and oral contraceptives are metabolized by hepatic P450 oxidase, but these two drugs neither induce nor inhibit the activity of P450 oxidase.

(Choices D, E and F) Fluconazole, cimetidine, and omeprazole inhibit P450 enzymes and increase the concentration of phenytoin in the serum.

Educational objective:
Phenytoin metabolism depends on the function of hepatic P450 oxidases and is dose-dependent. Drugs that induce hepatic microsomal enzymes (phenobarbital, carbamazepine, and rifampin) enhance phenytoin metabolism and decrease its serum concentration. You should know all of the commonly-prescribed medications that are metabolized by the P450 system, and you should know which drugs induce or inhibit the function of these enzymes.

References

2. Phenytoin is **an inducer of P450 oxidase**. Induction of this enzyme increases the consumption of many medications that are metabolized by the liver, such as oral contraceptives. When the P450 oxidase system is induced, the serum concentration of such medications will decrease, thereby reducing efficacy.
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References

- Cytochrome P450: new nomenclature and clinical implications
- Pharmacokinetic drug interactions with phenytoin (Part I).

Pharmacology	Nervous System	Antiepileptics
Subject	System	Topic

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A 38-year-old Caucasian female presents to your office because of sudden episodes of severe, right-sided facial pain. She describes the pain as "a knife stabbing my face." The pain lasts several seconds and is usually instigated by a meal or teeth brushing. There is no nausea or vomiting. She denies any visual changes. Her past medical history is significant for hyperlipidemia. She drinks alcohol socially and does not use tobacco. She has no family history of facial pain. Her vital signs are within normal limits, and physical examination shows no rash. Which of the following is the best initial treatment for this patient?

A. Baclofen
B. Haloperidol
C. Diazepam
D. Carbamazepine
E. Propranolol
F. Phenobarbital
G. Valproic acid

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A. Baclofen (13%)
B. Haloperidol (2%)
C. Diazepam (6%)
✓ D. Carbamazepine (64%)
E. Propranolol (4%)
F. Phenobarbital (3%)
G. Valproic acid (6%)

Omitted
Correct answer
D

64%
Answered correctly

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01/14/2020
Last Updated

Explanation

This case presents a classic picture of trigeminal neuralgia (tic douloureux). This condition presents with episodes of sudden and severe pain in the distribution of CN V (particularly V2 and V3). The pain is described as "stabbing" or like an "electrical shock"; it is usually unilateral, and does

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This case presents a classic picture of trigeminal neuralgia (tic douloureux). This condition presents with episodes of sudden and severe pain in the distribution of CN V (particularly V2 and V3). The pain is described as "stabbing" or like an "electrical shock"; it is usually unilateral, and does not last more than few seconds; but occurs repeatedly. Pain is triggered by any stimulus to CN V, for example chewing, teeth brushing, shaving or washing an affected area of the face, swallowing, or exposure to hot or cold temperatures. These painful episodes may occur for several months. In the majority of cases, trigeminal neuralgia is not caused by any structural abnormality and its pathogenesis remains unclear.

Carbamazepine is the drug of choice for the treatment of trigeminal neuralgia. It is effective in pain reduction in up to 80% of patients. Like phenytoin, it inhibits neuronal high-frequency firing by reducing the ability of sodium channels to recover from inactivation. Carbamazepine can cause aplastic anemia, so CBC should be monitored regularly. Carbamazepine is a P450 inducer that increases the metabolism of many other medications, thereby decreasing their effectiveness.

(Choices A and G) Baclofen and valproic acid can be used for trigeminal neuralgia, but are not first-line choices.

(Choice B) Haloperidol is a neuroleptic medication used for the treatment of schizophrenia, acute psychoses, acute mania, and Tourette syndrome. It is not indicated in trigeminal neuralgia.

(Choice E) Propranolol has various uses, including migraine prophylaxis and the reduction of portal venous pressure to prevent variceal bleed. It is not used for trigeminal neuralgia.

(Choice F) Phenobarbital is effective for the management of generalized tonic-clonic seizures. It is not used for trigeminal neuralgia.

Educational objective:
Trigeminal neuralgia presents with brief episodes of sudden and severe "electric shock-like" or "stabbing" pain in the distribution of CN V (particularly V2 and V3). Carbamazepine is the drug of choice.

References

- Trigeminal neuralgia and its management
- Drug therapy of trigeminal neuralgia

Pharmacology	Nervous System	Trigeminal neuralgia
Subject	System	Topic

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A 23-year-old man is evaluated for prolonged paralysis following general anesthesia for an elective surgical procedure. Anesthesia was induced with propofol, succinylcholine was used for intubation, and anesthesia was maintained via propofol and fentanyl infusions. The patient has not had a return of neuromuscular function after several hours. His mother then discloses that she has also been "slow to wake up" from anesthesia. Which of the following is the most likely reason for this patient's prolonged paralysis?

A. Decreased first-pass metabolism

B. Decreased plasma hydrolysis

C. Increased binding to plasma proteins

D. Increased redistribution to fat

E. Upregulation of target receptors

Submit

A 23-year-old man is evaluated for prolonged paralysis following general anesthesia for an elective surgical procedure. Anesthesia was induced with propofol, succinylcholine was used for intubation, and anesthesia was maintained via propofol and fentanyl infusions. The patient has not had a return of neuromuscular function after several hours. His mother then discloses that she has also been "slow to wake up" from anesthesia. Which of the following is the most likely reason for this patient's prolonged paralysis?

- A. Decreased first-pass metabolism (21%)
- ✓ B. Decreased plasma hydrolysis (39%)
- C. Increased binding to plasma proteins (8%)
- D. Increased redistribution to fat (14%)
- E. Upregulation of target receptors (15%)

Omitted
Correct answer
B

39%
Answered correctly

02 secs
Time Spent

04/10/2020
Last Updated

Explanation

This patient who developed prolonged muscle weakness (eg, failure of spontaneous respiration, voluntary muscle activity) after receiving succinylcholine most likely has pseudocholinesterase deficiency, an autosomal recessive disorder caused by a genetic polymorphism in the *BCHE* gene.

Succinylcholine is a depolarizing neuromuscular blocking agent used to induce skeletal muscle relaxation during intubation and surgery. It acts as a **competitive agonist** of **nicotinic acetylcholine receptors** of the motor endplate, where it induces **persistent depolarization**, leading to desensitization and skeletal muscle paralysis. Succinylcholine is rapidly **hydrolyzed by plasma pseudocholinesterase**; only around 10% of the

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Patients with **pseudocholinesterase deficiency** are unable to metabolize succinylcholine, which leads to a large amount of the drug reaching the neuromuscular junction. Heterozygotes may experience double the normal duration of paralysis; homozygotes can have persistent **paralysis for several hours**.

(Choice A) Decreased first-pass metabolism often occurs when drugs are administered via a nonoral route, allowing them to reach the systemic circulation without passing through the portal circulation and liver. Although succinylcholine is given intravenously, it is primarily inactivated in the plasma by pseudocholinesterase rather than the liver.

(Choice C) The pharmacologic effects of drugs are typically enacted by the unbound (free) form of the drug. Therefore, increased binding to plasma proteins would likely decrease (rather than increase) the effect of the medication.

(Choice D) Propofol is highly lipid soluble and has a very short duration of action (seconds) because of rapid redistribution from the brain (where it activates the GABA-A receptor) to other tissues (predominantly fat). However, propofol is a hypnotic agent; it does not cause muscle paralysis.

(Choice E) Upregulation of target receptors would increase sensitivity to acetylcholine, which is one possible mechanism of spasticity in cerebral palsy. However, receptor upregulation occurs over many hours or days, not with a first dose.

Educational objective:
Succinylcholine, a depolarizing neuromuscular blocking agent, is rapidly hydrolyzed by plasma pseudocholinesterase. Patients with pseudocholinesterase deficiency have prolonged neuromuscular paralysis after drug administration.

Pharmacology Nervous System Anesthesia

Succinylcholine is a depolarizing neuromuscular blocking agent used to induce skeletal muscle relaxation during intubation and surgery. It acts as a **competitive agonist** of **nicotinic acetylcholine receptors** of the motor endplate, where it induces **persistent depolarization**, leading to desensitization and skeletal muscle paralysis. Succinylcholine is rapidly **hydrolyzed by plasma pseudocholinesterase**; only around 10% of the administered dose reaches the neuromuscular junction, where it typically has a duration of action of <10 minutes.

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(Choice D) Propofol is highly lipid soluble and has a very short duration of action (seconds) because of rapid redistribution from the brain (where it activates the GABA-A receptor) to other tissues (predominantly fat). However, propofol is a hypnotic agent; it does not cause muscle paralysis.

(Choice E) Upregulation of target receptors would increase sensitivity to acetylcholine, which is one possible mechanism of spasticity in cerebral palsy. However, receptor upregulation occurs over many hours or days, not with a first dose.

Educational objective:
Succinylcholine, a depolarizing neuromuscular blocking agent, is rapidly hydrolyzed by plasma pseudocholinesterase. Patients with pseudocholinesterase deficiency have prolonged neuromuscular paralysis after drug administration.

Pharmacology	Nervous System	Anesthesia
Subject	System	Topic

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A 63-year-old man comes to the office due to blurred vision in both eyes for the last 2 days. The blurriness is worse when he reads but is not noticeable when he drives. The patient has no associated headache, double vision, or weakness. However, he did start taking diphenhydramine several days ago for seasonal allergies. Past medical history is unremarkable. Vital signs are normal. On physical examination, there is edema and clear drainage affecting the nasal mucosa. Funduscopic examination is normal. This patient's visual symptoms are most likely due to blockade of which of the following mediators?

A. Acetylcholine
B. Histamine
C. Leukotrienes
D. Norepinephrine
E. Serotonin

Submit

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- ✓ A. Acetylcholine (65%)
- B. Histamine (27%)
- C. Leukotrienes (1%)
- D. Norepinephrine (4%)
- E. Serotonin (0%)

Omitted
Correct answer
A

65%
Answered correctly

01 sec
Time Spent

02/12/2020
Last Updated

Explanation

This patient has impaired visual accommodation due to **anticholinergic** (anti-muscarinic) effects of **first-generation antihistamines** (eg, chlorpheniramine, diphenhydramine). Antihistamines are designed to relieve the allergic symptoms caused by release of histamine from mast cells (eg, rhinorrhea, itchy eyes and nose, urticaria). However, first-generation antihistamines can have prominent side effects due to blockade of other receptors, including alpha-adrenergic, serotonergic, and cholinergic receptors.

The ciliary muscle attaches to the lens via the zonular fibers. Contraction of the muscle reduces tension on the fibers, allowing the lens to become

Explanation

This patient has impaired visual accommodation due to **anticholinergic** (anti-muscarinic) effects of **first-generation antihistamines** (eg, chlorpheniramine, diphenhydramine). Antihistamines are designed to relieve the allergic symptoms caused by release of histamine from mast cells (eg, rhinorrhea, itchy eyes and nose, urticaria). However, first-generation antihistamines can have prominent side effects due to blockade of other receptors, including alpha-adrenergic, serotonergic, and cholinergic receptors.

The ciliary muscle attaches to the lens via the zonular fibers. Contraction of the muscle reduces tension on the fibers, allowing the lens to become more spherical and increasing its refractive power. The ciliary muscle is under parasympathetic control from the Edinger-Westphal nucleus/ciliary ganglion. Inhibition of this pathway by antimuscarinic agents will limit **accommodation** and cause blurring of vision for close objects. The pupillary sphincter also receives parasympathetic innervation from the Edinger-Westphal nucleus, and patients on antimuscarinic agents may have mydriasis (pupillary dilation) as well.

(Choice B) First-generation antihistamines easily cross the blood-brain barrier into the central nervous system, where they interfere with the normal neurotransmitter functions of histamine. Side effects can include drowsiness and cognitive dysfunction.

(Choice C) Leukotrienes are inflammatory mediators that contribute to nasal, ocular, and respiratory symptoms in patients with allergic disorders and asthma. Antihistamines do not interfere with leukotriene formation or action.

(Choice D) Alpha-adrenergic blockade causes peripheral vasodilation, resulting in hypotension and postural dizziness.

(Choice E) Serotonin receptor blockade by antihistamines causes appetite stimulation and weight gain.

Educational objective:
In addition to blocking histamine receptors, first-generation antihistamines (eg, chlorpheniramine, diphenhydramine) have antimuscarinic, anti-alpha adrenergic, and anti-serotonergic properties. Anticholinergic effects on the ocular ciliary muscles impair accommodation and cause blurring of vision for close objects.

Pharmacology	Nervous System	Antihistamines
Subject	System	Topic

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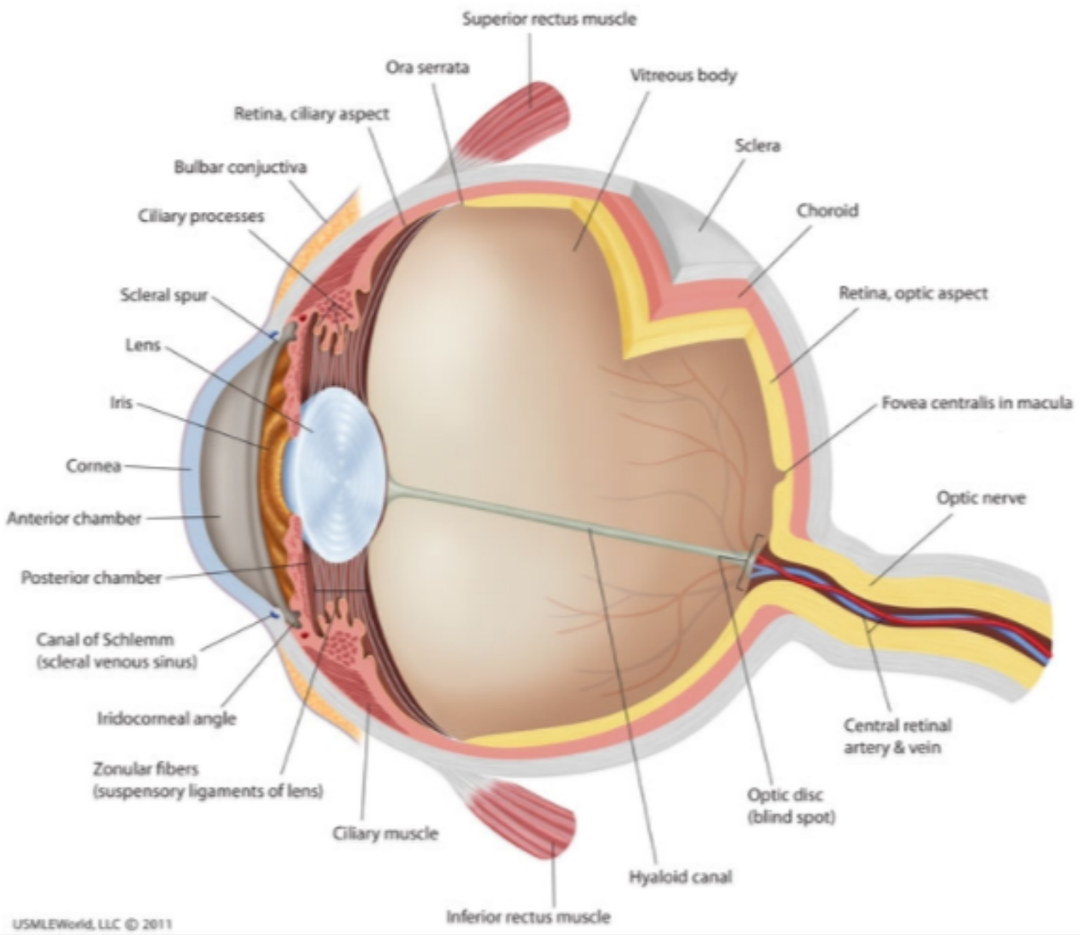
The Eye



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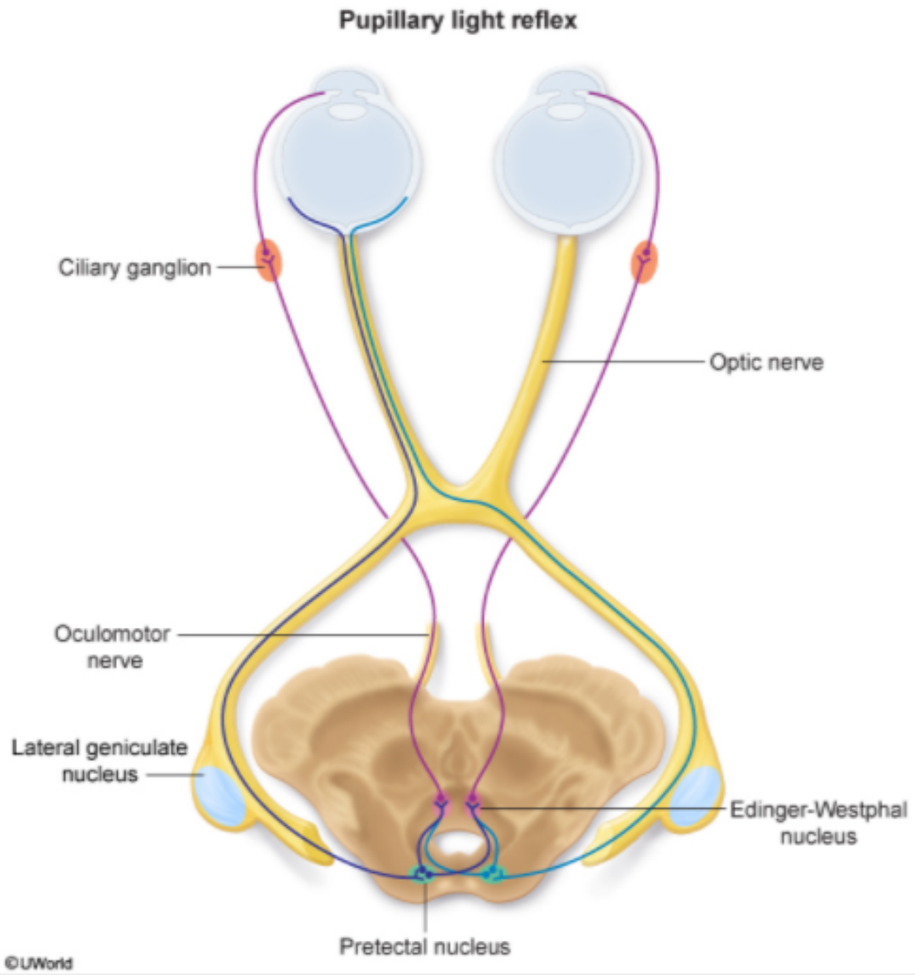

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A 45-year-old quadriplegic man with suspected bacterial pneumonia is admitted to the hospital and started on intravenous antibiotics. Over the next 24 hours, he develops progressive respiratory failure requiring mechanical ventilation. Prior to intubation, a skeletal muscle relaxant is administered and the patient subsequently goes into cardiac arrest. His attached cardiac monitor shows ventricular fibrillation. While he is being resuscitated, his serum potassium level is drawn and later comes back as 9.5 mEq/L. Administration of which of the following agents is most likely responsible for this patient's condition?

A. Atracurium
B. Baclofen
C. Dantrolene
D. Succinylcholine
E. Vecuronium

Submit

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A. Atracurium (5%)
B. Baclofen (7%)
C. Dantrolene (10%)
✓ D. Succinylcholine (70%)
E. Vecuronium (6%)

Omitted
Correct answer
D

70%
Answered correctly

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03/03/2020
Last Updated

Explanation

Adverse effects of succinylcholine

- Malignant hyperthermia (especially with halothane) in genetically susceptible patients

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Adverse effects of succinylcholine

- Malignant hyperthermia (especially with halothane) in genetically susceptible patients
- Severe hyperkalemia in patients with burns, myopathies, crush injuries, and denervation
- Bradycardia from parasympathetic stimulation or tachycardia from sympathetic effects

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Succinylcholine is a depolarizing neuromuscular-blocking agent that, like acetylcholine, attaches to the nicotinic acetylcholine receptor (nAChR) and depolarizes the neuromuscular end plate. Unlike acetylcholine, succinylcholine is not degraded by acetylcholinesterase, resulting in continuous stimulation of the endplate (reflected by initial transient fasciculations). However, the sodium channels surrounding the end plate rapidly become inactivated and cannot reopen until the end plate is repolarized. Thus, succinylcholine-induced depolarization remains isolated to the end plate, resulting in development of a flaccid paralysis (**phase 1 block**). Eventually, with continued administration of succinylcholine, the continuous depolarization of the endplate gives way to gradual repolarization as the nAChR becomes desensitized to the effects of succinylcholine. This is termed **phase II block** and is similar to non-depolarizing blockade.

Because the nAChR is a nonselective cation channel, its opening not only allows sodium influx but also potassium release. Exaggerated hyperkalemia and life-threatening arrhythmias can occur in patients with crush or burn injuries, denervating injuries or diseases (eg, quadriplegia and Guillain-Barré syndrome), and myopathies. These pathologic states cause up-regulation of muscle nAChRs and/or rhabdomyolysis, which can result in the release of large amounts of potassium when succinylcholine is administered. In these patients, non-depolarizing agents such as vecuronium or rocuronium are better choices (**Choice E**).

(Choice A) The nondepolarizing neuromuscular-blocking agent atracurium releases histamine and can produce a fall in blood pressure, flushing, and bronchoconstriction. It is also metabolized to laudanosine, which can provoke seizures.

(Choice B) Baclofen is a muscle relaxant that affects $GABA_B$ receptors at the level of the spinal cord.

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(Choice B) Baclofen is a muscle relaxant that affects $GABA_B$ receptors at the level of the spinal cord.

(Choice C) Dantrolene is a muscle relaxant effective in malignant hyperthermia. It acts on ryanodine receptors on the sarcoplasmic reticulum and prevents release of calcium into the cytoplasm of muscle fibers.

Educational objective:
Succinylcholine can cause significant potassium release and life-threatening arrhythmias in patients at high risk for hyperkalemia, including those with burns, myopathies, crush injuries, and denervating injuries or disease.

References

- Succinylcholine-induced hyperkalemia in acquired pathologic states: etiologic factors and molecular mechanisms.

Pharmacology	Nervous System	Neuromuscular blocker
Subject	System	Topic

A 75-year-old woman is brought to the emergency department after a syncopal episode at her assisted living facility. The event occurred an hour ago, when she was eating lunch with other residents of the facility. The patient suddenly slumped over onto the table and awakened spontaneously after about 30 seconds. She appeared pale afterwards but was not confused, and fingerstick blood glucose was normal. Medical history includes hypertension, type 2 diabetes mellitus, osteoporosis, osteoarthritis, and Alzheimer disease. Temperature is 37 C (98.6 F), supine blood pressure is 110/68 mm Hg, and pulse is 62/min. The oropharyngeal mucosa is moist and jugular venous pressure is normal. The lungs are clear on auscultation and heart sounds are normal. The patient is hospitalized for observation and is found to have an episodic bradyarrhythmia and atrioventricular block. If this patient's condition is due to a medication, which of the following is the most likely cause?

A. Amlodipine
B. Canagliflozin
C. Diphenhydramine
D. Donepezil
E. Lisinopril

Submit

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- A. Amlodipine (48%)
- B. Canagliflozin (3%)
- C. Diphenhydramine (13%)
- ✓ D. Donepezil (29%)
- E. Lisinopril (4%)

Omitted
Correct answer
D

29%
Answered correctly

02 secs
Time Spent

04/09/2020
Last Updated

Explanation

This patient's brief loss of consciousness is consistent with **syncope**, which occurs due to a **transient loss of cerebral perfusion**. Most episodes of syncope are benign, resulting from a vasovagal reflex that is triggered by emotional stress or prolonged standing. However, syncope may be a warning sign of a serious underlying pathology (eg, cardiac arrhythmia, severe aortic stenosis, pulmonary embolism). In addition, numerous

This patient's brief loss of consciousness is consistent with **syncope**, which occurs due to a **transient loss of cerebral perfusion**. Most episodes of syncope are benign, resulting from a vasovagal reflex that is triggered by emotional stress or prolonged standing. However, syncope may be a warning sign of a serious underlying pathology (eg, cardiac arrhythmia, severe aortic stenosis, pulmonary embolism). In addition, numerous **medications** can cause or contribute to syncope and should be considered.

Acetylcholinesterase inhibitors (eg, donepezil, rivastigmine) are commonly used in the management of Alzheimer dementia. Alzheimer dementia involves dysfunction of cholinergic pathways in the brain; therefore, inhibition of acetylcholinesterase and a consequent reduction in acetylcholine breakdown may improve cognitive function in some patients. However, this mechanism also produces **enhanced parasympathetic tone** that can lead to adverse effects. Underlying age-related degeneration of the conduction system is common in the elderly, and the effects of acetylcholinesterase inhibition can precipitate **bradycardia** and **atrioventricular block** in such patients. These conduction abnormalities lead to **reduced cardiac output** that may manifest as presyncope (ie, lightheadedness) or syncope.

(Choices A, B, C, and E) Antihypertensive agents such as amlodipine and lisinopril may contribute to orthostatic syncope (syncope that occurs with standing). By inhibiting vasoconstriction, these agents both prevent mobilization of venous blood that is pooled in the legs and impair the increase in arteriolar resistance needed to maintain cerebral perfusion on standing. First-generation histamine-1 blockers (eg, diphenhydramine) have alpha-1 receptor-blocking properties and may also contribute to orthostatic syncope via inhibited vasoconstriction. Sodium-glucose cotransporter-2 inhibitors (eg, canagliflozin) may contribute to orthostatic syncope by stimulating an osmotic diuresis that leads to hypovolemia. None of these agents cause syncope via the slowing of cardiac conduction.

Educational objective:
Syncope results from a transient loss of cerebral perfusion, and numerous medications can cause or contribute to syncope. Acetylcholinesterase inhibitors (eg, donepezil, rivastigmine) may cause syncope due to enhanced parasympathetic tone that leads to bradycardia and atrioventricular block with reduced cardiac output.

References

- Cholinesterase inhibitors and incidence of bradycardia in patients with dementia in the Veterans Affairs New England Healthcare System.

Pharmacology	Nervous System	Syncope
Subject	System	Topic

This patient's brief loss of consciousness is consistent with **syncope**, which occurs due to a **transient loss of cerebral perfusion**. Most episodes of syncope are benign, resulting from a vasovagal reflex that is triggered by emotional stress or prolonged standing. However, syncope may be a warning sign of a serious
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Educational objective:
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References

- Cholinesterase inhibit

Pharmacology — Subject
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Exhibit Display

Medication-induced orthostasis

Mechanism	Examples
α-1 blockade–mediated vasodilation	• Terazosin, prazosin, doxazosin • Antipsychotics (eg, risperidone) • Antihistamines, TCAs
Other vasodilation	• ACE inhibitors & ARBs • Dihydropyridine CCBs • Hydralazine, nitrates • Phosphodiesterase inhibitors
Volume depletion	• Diuretics • SGLT-2 inhibitors
Sympathetic blockade	• Beta blockers • Clonidine

ARBs = angiotensin receptor blockers; **CCBs** = calcium channel blockers; **SGLT** = sodium-glucose cotransporter; **TCAs** = tricyclic antidepressants.

Add To Flash Card

A 48-year-old woman with metastatic cervical cancer is brought to the emergency department due to worsening lethargy for the past several days. A year ago, the patient was diagnosed with cervical cancer, which has progressed despite chemotherapy treatment and metastasized to the liver and lungs. She has also developed bilateral hydronephrosis and renal failure due to ureteral compression by the tumor. The patient is receiving palliative care, and her pain has been adequately controlled with a stable dose of oral morphine. Temperature is 36.7 C (98 F), blood pressure is 110/62 mm Hg, pulse is 92/min, and respirations are 10/min. On physical examination, the patient is somnolent and responds to painful stimuli only. The pupils are small and sluggish to react. The lungs are clear to auscultation, and heart sounds are normal. The abdomen is soft and nondistended. Arterial blood gas analysis shows respiratory acidosis. Which of the following medication-related events most likely precipitated her current condition?

- A. Decreased first-pass metabolism
- B. Decreased hepatic metabolism
- C. Increased enterohepatic circulation
- D. Increased metabolite accumulation
- E. Increased volume of distribution

Submit

A 48-year-old woman with metastatic cervical cancer is brought to the emergency department due to worsening lethargy for the past several days. A year ago, the patient was diagnosed with cervical cancer, which has progressed despite chemotherapy treatment and metastasized to the liver and lungs. She has also developed bilateral hydronephrosis and renal failure due to ureteral compression by the tumor. The patient is receiving palliative care, and her pain has been adequately controlled with a stable dose of oral morphine. Temperature is 36.7 C (98 F), blood pressure is 110/62 mm Hg, pulse is 92/min, and respirations are 10/min. On physical examination, the patient is somnolent and responds to painful stimuli only. The pupils are small and sluggish to react. The lungs are clear to auscultation, and heart sounds are normal. The abdomen is soft and nondistended. Arterial blood gas analysis shows respiratory acidosis. Which of the following medication-related events most likely precipitated her current condition?

- A. Decreased first-pass metabolism (12%)
- B. Decreased hepatic metabolism (26%)
- C. Increased enterohepatic circulation (2%)
- ✓ D. Increased metabolite accumulation (53%)
- E. Increased volume of distribution (5%)

Omitted
Correct answer
D

53%
Answered correctly

02 secs
Time Spent

02/19/2020
Last Updated

Explanation

Morphine stimulates mu opioid receptors to provide the desired effect of analgesia, but in doing so can also precipitate many undesired effects. This patient has multiple signs of **opioid toxicity**, including miosis (ie, pinpoint pupils), **respiratory depression** (evidenced by slow respiratory

Morphine stimulates mu opioid receptors to provide the desired effect of analgesia, but in doing so can also precipitate many undesired effects. This patient has multiple signs of **opioid toxicity**, including miosis (ie, pinpoint pupils), **respiratory depression** (evidenced by slow respiratory rate and respiratory acidosis), and CNS depression (eg, **somnolence**, coma). Morphine is primarily metabolized by the liver via glucuronidation to form **2 major metabolites**. These metabolites, morphine-3-glucoronide and **morphine-6-glucoronide**, then undergo **renal elimination** via excretion in the urine. Because the metabolites are metabolically active, **renal dysfunction** can lead to **metabolite accumulation** and opioid toxicity. Morphine-6-glucoronide is particularly responsible for toxicity, acting as a more potent mu opioid receptor agonist than morphine itself.

Due to its metabolically active and renally cleared metabolites, morphine requires careful monitoring when used in patients with renal dysfunction. When opioid pain control is needed in such patients, fentanyl or hydromorphone is often preferred as these drugs are predominantly hepatically cleared.

(Choice A) Decreased first-pass metabolism occurs with drugs that are given by a route other than orally, allowing the drug to reach the systemic circulation without passing through the portal circulation and the liver. Examples include drugs that are administered sublingually, rectally, or intravenously.

(Choice B) Decreased hepatic metabolism is common in the elderly or in patients with advanced liver disease (eg, cirrhosis). Although this patient has metastatic disease to the liver, accumulation of morphine metabolites is a more likely cause of toxicity in the setting of known renal failure.

(Choice C) Enterohepatic circulation occurs when a drug undergoes biliary excretion into the small intestine, where it is then reabsorbed back into the bloodstream. Such drugs typically demonstrate a prolonged half-life. Although the phenomenon may account for a prolonged duration of therapeutic effect, it rarely accounts for toxicity.

(Choice E) Drugs with a high volume of distribution (eg, amiodarone) are well distributed in the tissues and have a long half-life. These drugs may demonstrate prolonged therapeutic and/or adverse effects after discontinuation.

Educational objective:
Morphine generates 2 major metabolites that are metabolically active and renally cleared. These metabolites can accumulate in the bloodstream of patients with renal dysfunction and lead to opioid toxicity, evidenced by miosis, respiratory depression, and CNS depression.

References

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Educational objective:
Morphine generates 2 major metabolites that are metabolically active and renally cleared. These metabolites can accumulate in the bloodstream of patients with renal dysfunction and lead to opioid toxicity, evidenced by miosis, respiratory depression, and CNS depression.

References

- Relationships among morphine metabolism, pain and side effects during long-term treatment: an update.

Pharmacology	Nervous System	Opioids
Subject	System	Topic

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A 14-year-old boy is brought to the physician by his mother for seizures. His seizures are usually characterized as a blank stare and lip smacking, followed by generalized shaking. The patient occasionally bites his tongue during the episodes and feels confused afterwards. His seizures have been refractory to various antiepileptic medications and he is going to be started on lamotrigine. The patient should be instructed to see his physician immediately if which of the following symptoms occurs?

A. Abdominal pain
B. Cough and fever
C. Diarrhea
D. Heartburn
E. Skin rash
F. Urine discoloration

Submit

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- A. Abdominal pain (4%)
- B. Cough and fever (4%)
- C. Diarrhea (1%)
- D. Heartburn (0%)
- ✓ E. Skin rash (78%)
- F. Urine discoloration (10%)

Omitted
Correct answer
E

78%
Answered correctly

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Time Spent

01/24/2020
Last Updated

Explanation

Lamotrigine is an anticonvulsant that works by blocking voltage-gated **sodium channels**. It can be used to treat partial and generalized seizures and is also effective for bipolar disorder.

Up to 10% of patients using lamotrigine will develop benign rash; however, a potentially life-threatening rash due to **Stevens-Johnson syndrome** (SJS) or **toxic epidermal necrolysis** (TEN) occurs in up to 1% of patients (particularly children). SJS and TEN represent different endpoints along the same disease continuum: SJS involves <10% of the body surface area and TEN has >30% involvement. Patients with SJS/TEN

Explanation

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The first appearance of rash requires discontinuation of the drug immediately as SJS/TEN and benign rash cannot be distinguished reliably. Other anticonvulsants associated with SJS/TEN include carbamazepine, phenobarbital, and phenytoin.

(Choices A, B, C, D, and F) Gastrointestinal symptoms (eg, abdominal pain, heartburn, diarrhea) are relatively common with lamotrigine and other anticonvulsant medications but are usually not life-threatening. Symptoms such as fever, cough, and urinary symptoms are rare.

Educational objective:
Lamotrigine can be used to treat partial and generalized seizures and works by blocking voltage-gated sodium channels. Stevens-Johnson syndrome and toxic epidermal necrolysis are rare, life-threatening adverse effects characterized by flu-like symptoms followed by widespread mucocutaneous epidermal necrosis.

References

- Predictors of Lamotrigine-associated rash.
- Efficacy and safety of lamotrigine monotherapy in children and adolescents with epilepsy.

Pharmacology	Nervous System	Antiepileptics
Subject	System	Topic

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Explanation

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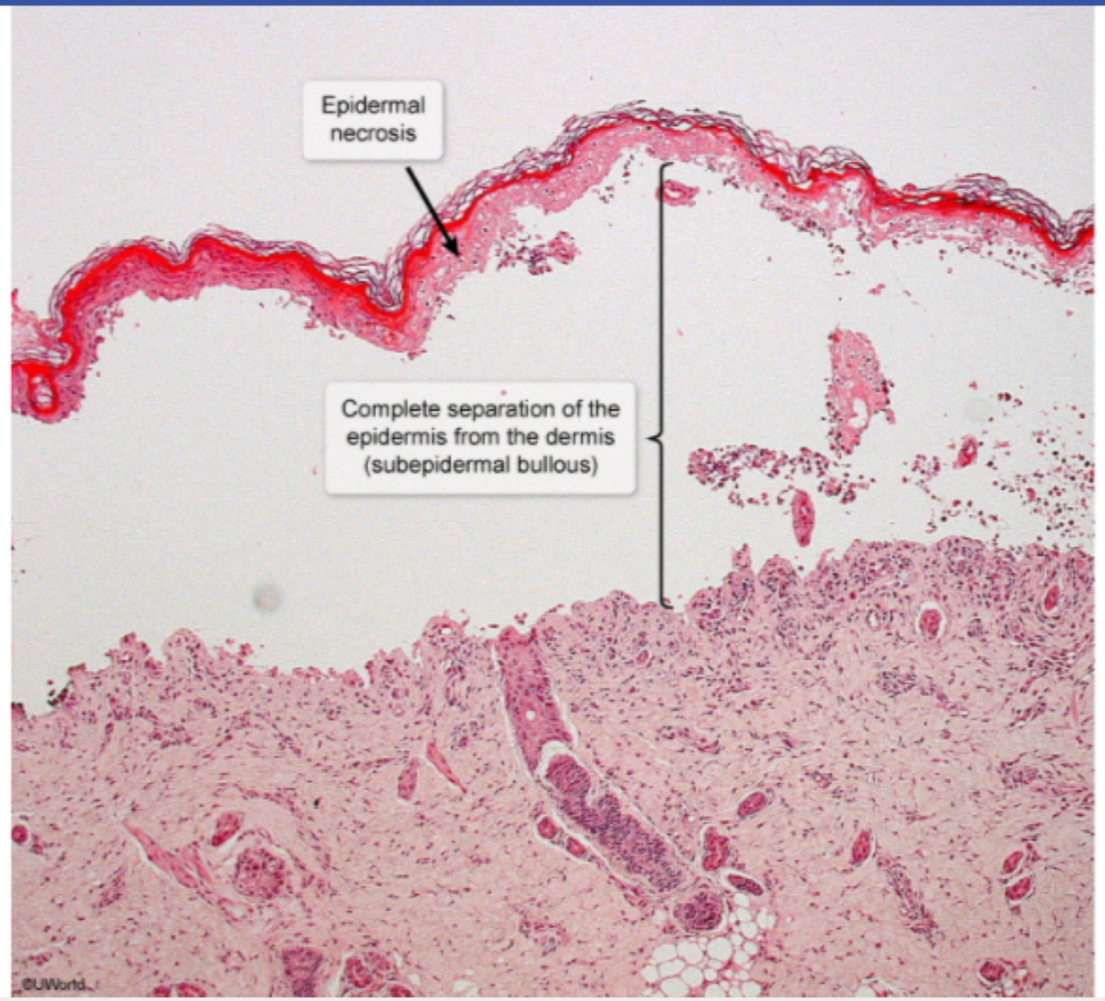

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A 25-year-old man is brought to the emergency department after being found unresponsive. He has a history of schizoaffective disorder and previous suicide attempts by prescription medication overdose. The patient was recently started on haloperidol and sertraline. Temperature is 40.6 C (105 F), blood pressure is 180/98 mm Hg, and pulse is 112/min. On examination, the patient is obtunded and diffusely rigid without clonus. Laboratory studies show serum creatinine of 3.2 mg/dL, creatine kinase of 75,000 U/L, and leukocytes of 16,000/mm^3. The antidote for this patient's current condition most likely has which of the following mechanisms of action?

A. Activation of presynaptic voltage-gated calcium channels of motor neurons

B. Antagonism of peripheral and central serotonin receptors

C. Blockade of central dopamine D2 receptors

D. Inhibition of acetylcholinesterase at the neuromuscular junction

E. Inhibition of calcium ion release from sarcoplasmic reticulum of skeletal muscle

Submit

A 25-year-old man is brought to the emergency department after being found unresponsive. He has a history of schizoaffective disorder and previous suicide attempts by prescription medication overdose. The patient was recently started on haloperidol and sertraline. Temperature is 40.6 C (105 F), blood pressure is 180/98 mm Hg, and pulse is 112/min. On examination, the patient is obtunded and diffusely rigid without clonus. Laboratory studies show serum creatinine of 3.2 mg/dL, creatine kinase of 75,000 U/L, and leukocytes of 16,000/mm^3. The antidote for this patient's current condition most likely has which of the following mechanisms of action?

A. Activation of presynaptic voltage-gated calcium channels of motor neurons (3%)

B. Antagonism of peripheral and central serotonin receptors (19%)

C. Blockade of central dopamine D2 receptors (10%)

D. Inhibition of acetylcholinesterase at the neuromuscular junction (6%)

✓ E. Inhibition of calcium ion release from sarcoplasmic reticulum of skeletal muscle (60%)

Omitted
Correct answer
E

60%
Answered correctly

02 secs
Time Spent

02/11/2020
Last Updated

Explanation

Neuroleptic malignant syndrome	
Signs/symptoms	• Fever (>40 C common) • Confusion • Muscle rigidity (generalized)

Explanation

Neuroleptic malignant syndrome	
Signs/symptoms	• Fever (>40 C common) • Confusion • Muscle rigidity (generalized) • Autonomic instability (abnormal vital signs, sweating)
Treatment	• Stop antipsychotics or restart dopamine agents • Supportive care (hydration, cooling), intensive care unit • Dantrolene or bromocriptine if refractory

This patient has **neuroleptic malignant syndrome** (NMS) likely caused by an overdose of haloperidol. NMS is a life-threatening adverse reaction most commonly resulting from the use of **antipsychotics** (neuroleptic) medications, which block dopamine receptors in the brain. NMS presents clinically with **diffuse muscle rigidity**, **high fever**, **autonomic instability** (hypertension, tachycardia), and altered sensorium. Laboratory findings include **creatine kinase elevation** due to rhabdomyolysis, which can result in acute renal failure.

The mainstay of treatment is to discontinue the causative agent and provide supportive care (eg, intravenous hydration). In severe cases, **dantrolene** can be administered, which antagonizes ryanodine receptors and inhibits calcium release from the sarcoplasmic reticulum. Bromocriptine, a dopamine agonist, has also shown clinical benefit in NMS.

(Choice A) Activation of presynaptic voltage-gated calcium channels at the neuromuscular junction will trigger calcium influx into the terminal bulb. This will increase the release of acetylcholine from the terminal bulb onto the muscle endplate and, therefore, promote skeletal muscle contraction.

(Choice B) Serotonin receptor antagonists (eg, cyproheptadine) can be used to treat serotonin syndrome. Similar to NMS, serotonin syndrome can present with altered mental status and autonomic instability (diaphoresis, hypertension, hyperthermia, tachycardia). However, serotonin syndrome commonly presents with *hyperreflexia and myoclonus* (not diffuse rigidity) and gastrointestinal symptoms (nausea, diarrhea, vomiting).

(Choice C) Blockade of central dopamine D2 receptors in the brain leads to the extrapyramidal symptoms (eg, diffuse rigidity) observed in NMS.

The mainstay of treatment is to discontinue the causative agent and provide supportive care (eg, intravenous hydration). In severe cases, **dantrolene** can be administered, which antagonizes ryanodine receptors and inhibits calcium release from the sarcoplasmic reticulum. Bromocriptine, a dopamine agonist, has also shown clinical benefit in NMS.

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(Choice C) Blockade of central dopamine D2 receptors in the brain leads to the extrapyramidal symptoms (eg, diffuse rigidity) observed in NMS.

(Choice D) Inhibition of acetylcholinesterase results in increased acetylcholine at the neuromuscular junction, promoting skeletal muscle activation and contraction. Procholinergic agents should be avoided in NMS as they may exacerbate symptoms.

Educational objective:
Neuroleptic malignant syndrome is a life-threatening reaction to antipsychotic medications characterized by diffuse muscle rigidity, hyperthermia, autonomic instability, and altered sensorium. The antipsychotic should be stopped and supportive care provided; dantrolene, a ryanodine receptor blocker that inhibits calcium release from the sarcoplasmic reticulum, is an effective antidote.

References

- Neuroleptic malignant syndrome: a neuro-psychiatric emergency: recognition, prevention, and management.
- Serotonin syndrome vs neuroleptic malignant syndrome: a contrast of causes, diagnoses, and management.

Pharmacology	Nervous System	Neuroleptic malignant syndrome
Subject	System	Topic

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A 65-year-old man is brought to the emergency department after developing sudden-onset right-side weakness and difficulty speaking. He has a history of paroxysmal atrial fibrillation and has been taking warfarin for the past several years with a stable prothrombin time. His wife adds that he started taking a new drug 2 weeks ago, but she does not remember its name. Physical examination shows right hemiplegia, right hemisensory loss, expressive aphasia, and right homonymous hemianopia. MRI of the head shows a left middle cerebral artery territory infarct. Transesophageal echocardiogram reveals a small thrombus in the left atrium. This patient most likely started taking which of the following drugs recently?

A. Amiodarone
B. Cimetidine
C. Ciprofloxacin
D. Clarithromycin
E. Fluconazole
F. Penicillin V
G. St John's wort

Submit

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A. Amiodarone (10%)
B. Cimetidine (14%)
C. Ciprofloxacin (3%)
D. Clarithromycin (3%)
E. Fluconazole (4%)
F. Penicillin V (0%)
✓ G. St John's wort (61%)

Omitted
Correct answer
G

61%
Answered correctly

02 secs
Time Spent

04/20/2020
Last Updated

Explanation

Cytochrome P450 (CYP450)	
Inducers	**Inhibitors**
Carbamazepine Barbiturates Phenytoin Rifampin Griseofulvin St John's wort Modafinil Cyclophosphamide	Amiodarone Cimetidine Fluoroquinolones Clarithromycin Azole antifungals Grapefruit juice Isoniazid Ritonavir (protease inhibitors)

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This patient has suffered a **thromboembolic stroke**, likely the result of a dislodged left atrial thrombus that formed due to an adverse drug interaction leading to **inadequate anticoagulation**. Many substances cause induction or inhibition of cytochrome P450 (CYP450) hepatic microsomal enzymes, which are responsible for the majority of drug metabolism. CYP450 interactions should be considered when selecting and dosing medications, as changes in enzyme activity affect the rate of drug metabolism.

Alterations in plasma drug levels are especially important when considering medications that are vital to a patient's health or have a high propensity for toxicity, such as warfarin. For example, **warfarin** can interact with **St John's wort**, an over-the-counter medicinal herb known for both its anti-inflammatory and antidepressant properties. St John's wort **induces hepatic CYP450 enzymes**, resulting in increased warfarin metabolism, decreased drug levels, and inadequate anticoagulation.

(Choices A, B, C, D, and E) These drugs are known to inhibit CYP450 enzymes and increase warfarin levels, leading to an increased risk of bleeding complications.

(Choice F) Oral penicillin V and warfarin do not have any significant interactions. Antibiotics in general reduce the intestinal bacterial load, which reduces vitamin K synthesis and could potentiate warfarin's anticoagulant effects.

Modafinil Cyclophosphamide	Isoniazid Ritonavir (protease inhibitors)

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This patient has suffered a **thromboembolic stroke**, likely the result of a dislodged left atrial thrombus that formed due to an adverse drug interaction leading to **inadequate anticoagulation**. Many substances cause induction or inhibition of cytochrome P450 (CYP450) hepatic microsomal enzymes, which are responsible for the majority of drug metabolism. CYP450 interactions should be considered when selecting and dosing medications, as changes in enzyme activity affect the rate of drug metabolism.

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(Choice F) Oral penicillin V and warfarin do not have any significant interactions. Antibiotics in general reduce the intestinal bacterial load, which reduces vitamin K synthesis and could potentiate warfarin's anticoagulant effects.

Educational objective:
St John's wort induces cytochrome P450 hepatic microsomal enzymes. As a result, a wide variety of drugs that are metabolized by these enzymes, such as warfarin, will have lower plasma concentrations and decreased efficacy.

References

- Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects.

Pharmacology	Nervous System	Anticoagulants
Subject	System	Topic

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A 65-year-old Caucasian male presents to your office with increasing muscle rigidity and gait instability. He was diagnosed with Parkinson disease two years ago and has been treated with selegiline. His past medical history is otherwise insignificant. His father suffered from Parkinson disease and his mother died of an extensive stroke. You consider switching to levodopa to control this patient's symptoms adequately and discuss the adverse effect profile of levodopa with him. Which of the following adverse effects is most likely to persist after adding carbidopa to levodopa treatment?

A. Nausea and vomiting
B. Tachyarrhythmias
C. Hot flashes
D. Postural hypotension
E. Anxiety and agitation

Submit

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- A. Nausea and vomiting (20%)
- B. Tachyarrhythmias (12%)
- C. Hot flashes (5%)
- D. Postural hypotension (16%)
- ✓ E. Anxiety and agitation (44%)

Omitted
Correct answer
E

44%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

Anxiety and agitation are central effects of dopamine and are caused by L-dopa, regardless of whether carbidopa is added to levodopa treatment. In fact, anxiety and agitation can be increased because more dopamine is available to the brain. (Adding carbidopa inhibits the peripheral conversion of levodopa, making more of it available to the brain.) High-dose combination levodopa/carbidopa can cause various behavioral changes such as anxiety, agitation, insomnia, confusion, delusions, and hallucinations. Reducing the dose is helpful in alleviating these adverse effects. If reduced dosage is not possible, atypical antipsychotics, such as clozapine, may be helpful.

Correct answer
E

Answered correctly

Time Spent

Last Updated

Explanation

Anxiety and agitation are central effects of dopamine and are caused by L-dopa, regardless of whether carbidopa is added to levodopa treatment. In fact, anxiety and agitation can be increased because more dopamine is available to the brain. (Adding carbidopa inhibits the peripheral conversion of levodopa, making more of it available to the brain.) High-dose combination levodopa/carbidopa can cause various behavioral changes such as anxiety, agitation, insomnia, confusion, delusions, and hallucinations. Reducing the dose is helpful in alleviating these adverse effects. If reduced dosage is not possible, atypical antipsychotics, such as clozapine, may be helpful.

(Choice A) Nausea and vomiting are seen in up to 80% of patients when levodopa is used alone. Dopamine stimulates the emetic center located in the brainstem (which is outside of the blood brain barrier). Adding a dopa decarboxylase inhibitor reduces nausea and vomiting and significantly increases patient compliance. Most patients develop tolerance to nausea after several months.

(Choice B) Tachyarrhythmias, such as ventricular extrasystoles and atrial fibrillation, are attributed to the increased peripheral formation of catecholamines. Adding a peripheral decarboxylase inhibitor reduces these arrhythmias.

(Choices C and D) Postural hypotension and hot flashes also result from the peripheral conversion of levodopa to dopamine, so a peripheral decarboxylase inhibitor would decrease these problems.

Educational Objective:
Adding carbidopa can reduce most of the peripheral side effects of levodopa. However, behavioral changes from levodopa can actually worsen with addition of carbidopa because more dopamine becomes available to the brain.

Pharmacology	Nervous System	Parkinson disease
Subject	System	Topic

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A medical research center is studying therapeutic options for the treatment of neuromuscular disorders. During experimentation, scientists develop a new drug that seems to have partial agonist/antagonist activity against receptor X. When the experimental drug is applied to cells expressing receptor X, there is an immediate change in transmembrane calcium, sodium, and potassium flow secondary to the opening of the receptor channel. Receptor X is most likely which type of receptor?

A. α1 adrenoreceptor

B. β1 adrenoreceptor

C. β2 adrenoreceptor

D. Muscarinic cholinergic receptor

E. Nicotinic cholinergic receptor

Submit

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A. α1 adrenoreceptor (5%)

B. β1 adrenoreceptor (13%)

C. β2 adrenoreceptor (3%)

D. Muscarinic cholinergic receptor (19%)

✓ E. Nicotinic cholinergic receptor (57%)

Omitted
Correct answer
E

57%
Answered correctly

02 secs
Time Spent

04/07/2020
Last Updated

Explanation

Cell membrane receptors can be divided into two broad categories: ionotropic receptors (ion channels that open directly upon ligand binding) and metabotropic receptors (these receptors utilize second messengers to indirectly influence their corresponding ion channels). Nicotinic cholinergic receptors of the neuromuscular junction are an example of a ligand-gated ion channel receptor (ionotropic receptor). As an action potential progresses to the presynaptic terminal, voltage-gated calcium channels open and allow entry of calcium into the nerve cytoplasm. This triggers the fusion of storage vesicles with the membrane, allowing a release of acetylcholine (ACh). This ACh diffuses across the synaptic cleft and ultimately interacts with nicotinic cholinergic receptors present on the motor end plate. These receptors are ion channels that are comprised of

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Nicotinic cholinergic receptors are also found in the CNS and on postganglionic neurons of autonomic ganglia. The description in the question stem most likely represents a nicotinic cholinergic receptor given the **immediate** flux of sodium, calcium, and potassium demonstrated by the scientists.

(Choice A) Binding of epinephrine to α1 adrenoceptors results in the activation of the inositol triphosphate (IP_3) pathway. This pathway results in increased intracellular calcium via release of Ca^{2+} from storage organelles.

(Choices B & C) β1 and β2 adrenoceptors are associated with the cAMP signal transduction pathway. Stimulation of these receptors causes protein kinase A activation.

(Choice D) M1 and M3 muscarinic receptors utilize the inositol triphosphate pathway to increase intracellular calcium concentration and activate protein kinase C. M2 muscarinic receptors act via the cAMP second messenger system, and when activated decrease intracellular cAMP concentrations.

Educational objective:
The autonomic nervous system utilizes three types of signal pathways: cAMP, IP_3, and ion channels. Nicotinic receptors are ligand-gated ion channels that open after binding acetylcholine. This results in an immediate influx of Na^+ and Ca^{2+} into the cell and an outflux of K^+ from the cell.

References

- Neuromuscular junction in health and disease.

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References

- Neuromuscular junction in health and disease.

Pharmacology	Nervous System	Autonomic nervous system
Subject	System	Topic

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A 64-year-old man comes to the office with 2 months of episodic facial pain. He describes sudden-onset, severe, electric shock-like pain over the right cheek and ear lasting several seconds. The patient reports that activities like shaving and washing his face can trigger the pain and it is becoming more frequent. He is a retired veteran and has a history of posttraumatic stress disorder. Physical examination, including neurologic examination, is normal. Laboratory studies for blood cell counts, electrolytes, and hepatic and renal function are normal. The patient is started on a single drug therapy. On a follow-up visit 3 months later, he reports symptom improvement but is found to have the following blood counts:

Hemoglobin	9.0 g/dL
Reticulocytes	0.1%
Platelets	80,000/mm^3
Leukocytes	2,500/mm^3

Which of the following is the most likely mechanism of action of the drug used in this patient?

A. Blocks NMDA receptors in hippocampal neurons
B. Blocks serotonin reuptake on multiple levels
C. Decreases calcium current in thalamic neurons
D. Decreases sodium current on multiple levels
E. Increases chloride current on multiple levels
F. Inhibits synaptic acetylcholinesterase in cortical neurons

Submit

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Reticulocytes	0.1%
Platelets	80,000/mm^3
Leukocytes	2,500/mm^3

Which of the following is the most likely mechanism of action of the drug used in this patient?

- A. Blocks NMDA receptors in hippocampal neurons (6%)
- B. Blocks serotonin reuptake on multiple levels (9%)
- C. Decreases calcium current in thalamic neurons (8%)
- ✓ D. Decreases sodium current on multiple levels (66%)
- E. Increases chloride current on multiple levels (7%)
- F. Inhibits synaptic acetylcholinesterase in cortical neurons (1%)

Omitted
Correct answer
D

66%
Answered correctly

02 secs
Time Spent

05/12/2020
Last Updated

Explanation

This patient has **trigeminal neuralgia** (tic douloureux), a neuropathic disorder that typically presents with episodic, severe, unilateral, electric shock-like pain in the distribution of CN V. Symptoms are often triggered by innocuous stimuli such as shaving or washing the face. The first-line treatment of trigeminal neuralgia is **carbamazepine**, a neuroleptic medication that inhibits neuronal high-frequency firing by reducing the ability of **sodium channels** to recover from inactivation.

Carbamazepine may cause the following important adverse effects:

1. **Bone marrow suppression**, which may lead to anemia, agranulocytosis, and thrombocytopenia (complete blood cell counts should be monitored periodically)
2. Syndrome of inappropriate antidiuretic hormone secretion leading to hyponatremia

(Choice A) Ketamine, felbamate, and memantine are examples of medications that block NMDA receptors. Ketamine is used as a general anesthetic agent, felbamate is an anticonvulsant, and memantine may be effective in the treatment of Alzheimer dementia.

(Choice B) Selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline) are typically used to treat depression, anxiety, and posttraumatic stress disorder. Side effects may include headache, worsening anxiety/agitation, and insomnia.

(Choice C) Ethosuximide blocks T-type Ca^{2+} channels and decreases calcium current in thalamic neurons. This anticonvulsant is the agent of choice for absence seizures. Major side effects include gastrointestinal symptoms and drowsiness.

(Choice E) Various antiseizure medications (eg, benzodiazepines, barbiturates) act on the GABA-A receptor to increase chloride conductance; however, carbamazepine does not significantly affect chloride channels.

(Choice F) Donepezil is an acetylcholinesterase inhibitor that can be used to treat Alzheimer dementia. Side effects are generally related to increased cholinergic activity, which includes gastrointestinal symptoms and symptomatic bradycardia.

Educational objective:
The first-line treatment for trigeminal neuralgia is carbamazepine, a neuroleptic medication that inhibits neuronal high-frequency firing by reducing the ability of sodium channels to recover from inactivation. Carbamazepine can cause bone marrow suppression; therefore, complete blood cell counts should be monitored periodically.

monitored periodically)

2. Syndrome of inappropriate antidiuretic hormone secretion leading to hyponatremia

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References

- A review of carbamazepine's hematologic reactions and monitoring recommendations.
- Carbamazepine side effects in children and adults.

Pharmacology	Nervous System	Trigeminal neuralgia
Subject	System	Topic

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A 28-year-old man is undergoing a laparoscopic appendectomy for acute appendicitis. Shortly after induction of anesthesia, the surgeon reports difficulty maintaining abdominal insufflation due to severe muscle rigidity. Pulse is 130/min and the ECG tracing shows sinus tachycardia. Physical examination reveals diffuse muscle stiffness. Inhibition of which of the following is most likely to improve this patient's condition?

A. Acetylcholine degradation in cholinergic synapses

B. Alpha-receptor–mediated sympathetic activity

C. GABA-mediated neuron hyperpolarization

D. Ligand-receptor interaction in cholinergic synapses

E. Sarcoplasmic calcium release in skeletal muscles

Submit

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- A. Acetylcholine degradation in cholinergic synapses (10%)
- B. Alpha-receptor–mediated sympathetic activity (1%)
- C. GABA-mediated neuron hyperpolarization (3%)
- D. Ligand-receptor interaction in cholinergic synapses (10%)
- ✓ E. Sarcoplasmic calcium release in skeletal muscles (73%)

Omitted
Correct answer
E

73%
Answered correctly

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Time Spent

04/01/2020
Last Updated

Explanation

Malignant hyperthermia	
Pathophysiology	• Genetic mutation of ryanodine receptors • Triggered by inhalational anesthetics & succinylcholine • Unregulated sarcoplasmic calcium release → sustained muscle contraction
	• Masseter muscle spasm • Widespread muscle contraction (rigidity)

Malignant hyperthermia	
Pathophysiology	• Genetic mutation of ryanodine receptors • Triggered by inhalational anesthetics & succinylcholine • Unregulated sarcoplasmic calcium release → sustained muscle contraction
Clinical manifestations	• Masseter muscle spasm • Widespread muscle contraction (rigidity) • Hypercarbia • Rhabdomyolysis → hyperkalemia & acute renal failure • Hyperthermia (late manifestation)
Treatment	• Immediate cessation of causative anesthetic • Dantrolene

During laparoscopic procedures, small incisions are created to insert instruments into the abdominal cavity. Gas is insufflated to allow better visualization and easier access to organs while operating. Difficulty maintaining abdominal insufflation due to muscle contraction is often caused by insufficient doses of paralytic agents. However, if the patient has been appropriately medicated, sustained muscle contraction, especially when widespread, may be due to **malignant hyperthermia** (MH).

MH is often due to abnormal ryanodine receptors (*RYR1*) in the skeletal muscle. On exposure to certain anesthetic agents (typically succinylcholine and inhalational gases), these abnormal receptors allow the unregulated passage of calcium from the sarcoplasmic reticulum into the intracellular space. As a result of excessive calcium accumulation, patients develop sudden-onset, **widespread muscle rigidity**. Sustained muscle contraction **produces excessive CO_2**, leading to hypercarbia and acidosis; depletes cellular oxygen, leading to lactic acid production; and causes **muscle breakdown**, leading to rhabdomyolysis. **Hyperthermia** is often a later clinical sign that develops as the increased cellular metabolism overwhelms the body's ability to dissipate heat.

Many pharmacologic muscle relaxants work upstream from the pathologic process of excessive calcium release and are therefore ineffective during an acute MH crisis. **Dantrolene** is used to treat MH because it directly **inhibits intracellular calcium release** from the abnormal ryanodine receptor (*RYR1*).

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	• Dantrolene

During laparoscopic procedures, small incisions are created to insert instruments into the abdominal cavity. Gas is insufflated to allow better visualization and easier access to organs while operating. Difficulty maintaining abdominal insufflation due to muscle contraction is often caused by insufficient doses of paralytic agents. However, if the patient has been appropriately medicated, sustained muscle contraction, especially when widespread, may be due to **malignant hyperthermia** (MH).

MH is often due to abnormal ryanodine receptors (*RYR1*) in the skeletal muscle. On exposure to certain anesthetic agents (typically succinylcholine and inhalational gases), these abnormal receptors allow the unregulated passage of calcium from the sarcoplasmic reticulum into the intracellular space. As a result of excessive calcium accumulation, patients develop sudden-onset, **widespread muscle rigidity**. Sustained muscle contraction **produces excessive CO_2**, leading to hypercarbia and acidosis; depletes cellular oxygen, leading to lactic acid production; and causes **muscle breakdown**, leading to rhabdomyolysis. **Hyperthermia** is often a later clinical sign that develops as the increased cellular metabolism overwhelms the body's ability to dissipate heat.

Many pharmacologic muscle relaxants work upstream from the pathologic process of excessive calcium release and are therefore ineffective during an acute MH crisis. **Dantrolene** is used to treat MH because it directly **inhibits intracellular calcium release** from the abnormal ryanodine receptor (*RYR1*).

(Choice A) Neostigmine is an acetylcholinesterase inhibitor that prevents the degradation of acetylcholine in the neuromuscular junction. Therefore, it could increase, rather than decrease, the strength of muscle contractions.

(Choice B) Alpha-adrenergic antagonists (eg, phentolamine, phenoxybenzamine) inhibit alpha-receptor–mediated sympathetic activity. They are used primarily to lower blood pressure by decreasing vascular tone; they have minimal effect on skeletal muscle.

(Choices C and D) Baclofen is a GABA-B agonist that increases neuron hyperpolarization in the CNS to relax muscles. Nondepolarizing neuromuscular blocking agents (eg, rocuronium) are nicotinic receptor antagonists that inhibit the action of acetylcholine at the motor endplate. Both agents work upstream from intracellular calcium release and therefore have minimal impact on muscle contraction during an MH crisis.

Educational objective:
Malignant hyperthermia presents with widespread muscle rigidity after administration of inhalation anesthetics and/or succinylcholine to genetically susceptible individuals. It is treated with dantrolene, which blocks ryanodine receptors to prevent the release of calcium from the sarcoplasmic reticulum into the cytoplasm of skeletal muscle fibers.

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References

- Malignant hyperthermia, a Scandinavian update.

Pharmacology	Nervous System	Malignant hyperthemia
Subject	System	Topic

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